UNIV. OF
TORONTO
LIBRARY

Digitized by the Internet Archive
in 2010 with funding from
University of Toronto

http://www.archive.org/details/proceedings19newy

744

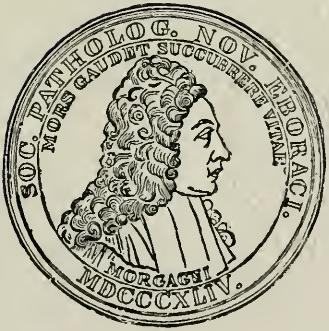
PROCEEDINGS

OF THE

NEW YORK PATHOLOGICAL SOCIETY

NEW SERIES, VOLUME XIX

1919


SOC. PATHOLOG. NOV. EBORACI.
MORS GAUDET SUCCURRERE VITAE.
MORGAGNI
MDCCCXLIV.

212281
18:5:27

Organized in 1844 Incorporated in 1886

NEW YORK
1919

PRESS OF
THE NEW ERA PRINTING COMPANY
LANCASTER, PA.

/

Proceedings

of the

New York Pathological Society

New Series, Vol. XIX JANUARY-MAY, 1919 Nos. 1-5

CONTENTS

PAGE

Fibroadenoma of the Umbilicus; Myositis Ossificans; Lymphosarcoma of the Appendix in a Child; Primary Carcinoma of the Fallopian Tube. *G. L. Rohdenburg, M.D.* 1

A Case of Von Jaksch's Anemia Occurring in a Child Five and One-half Months Old. *William C. Thro, M.D.* 6

Vaquez's Disease. *Douglas Symmers, M.D., and E. Applebaum* 10

Pulmonary Lesions of Influenza Pneumonia, and a Method of Museum Preparation. *James Ewing, M.D.* 15

The Relationship of *B. Influenzæ* to Clinical Influenza. *F. M. Huntoon, M.D., and S. Hannum* 22

Two Unusual Cases of Melanocarcinoma. *H. A. Murray, M.D.* 28

Report of a Case of Cyst of the Testicle in a Dog. *Alvan L. Barach, M.D.* 38

A Case of Chronic Cecitis of Unknown Origin. *A. O. Wilensky* 51

Sugar Tolerance in Cancer. *G. L. Rohdenburg, M.D., Adolph Bernhard, B.S., and Otto Krehbiel, M.D.* 54

The Production of Nonspecific Bactericidal Substances by Means of Staphylococcus and Streptococcus Vaccines in Vivo and in Vitro. *R. Ottenberg, M.D., and K. Wallach* 55

Carcinoma of the Uterus in a Mouse. *William H. Woglom, M.D.* 60

Congenital Bilateral Stricture of the Ureter. *Isidor Mufson, M.D.* 66

Extensive Bone Formation in the Thyroid. *H. Willy Meyer, M.D.* 70

Chorioepithelioma of Fallopian Tube; Embryonal Carcinoma of Ovary; Carcinoma of Rectum in a Boy of Sixteen. *L. W. Strong, M.D.* ... 71

A Case of Carcinoma of the Tube and a Case of Carcinoma of the Ovary. *Emil Schwartz, M.D.* 72

Eosinophilic (Polymorphonuclear) Leukemia. *Louis G. Shapiro, M.D.* .. 73

Is there a Parallelism between Normal Agglutinins and Hemolysins of Human Blood? *Reuben Ottenberg, M.D., and Frances Krasnow, A.M.* 83

DR. E. MOSCHCOWITZ, *President.*

FIBROADENOMA OF THE UMBILICUS; MYOSITIS OSSIFICANS; LYMPHOSARCOMA OF THE APPENDIX IN A CHILD; PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

G. L. ROHDENBURG, M.D.

(*From the Pathological Laboratory of the Lenox Hill Hospital in the City of New York*)

The first specimen, one of fibroadenoma of the umbilicus, has the following history: The patient was a woman aged 45, who noticed that for several years past there had gradually developed a mass in the umbilicus which gave rise to no pain or discomfort. She was under the impression that it arose after a violent effort at lifting a trunk. She was admitted to the hospital with a diagnosis of umbilical hernia which probably contained adherent omentum. At operation it was found that no hernia existed, but that the mass, which measured 8 × 10 cm., consisted of a new growth. On section this new growth showed alternating areas of what appeared to be fatty tissue and fibrous bands, with here and there small cysts.

Microscopical examination showed the tumor to be composed of acini lined by a single layer of high columnar epithelium with the acinar spaces at times filled with the products of secretion. These acini occurred in groups and were surrounded by rather dense zones of round cell infiltration. The various groups of acini in turn were supported by a dense and rather hyaline connective tissue. Malignant transformation of the epithelial or connective tissue elements was not demonstrable.

The origin of these growths has already been pointed out by several observers, notably by Cullen. They are embryonal in origin, being derived from the same source as Meckel's diverticulum.

The second specimen is one of primary lymphosarcoma of the appendix occurring in a four-year-old child. The history given briefly was that usual to an acute inflammation of the appendix. At the time of operation it was thought that the appendix had become invaginated into the cecum and an unsuccessful attempt was made to reduce the supposed invagination. This failing, a portion of the cecum was resected with the appendix. The gross specimen consisted of a portion of the cecum and appendix. It was peculiar in that the base of the appendix was apparently invaginated into the cecum, but on section the supposed invagination was shown to be a new growth involving the proximal one third of the appendix, and extending into the wall of the cecum in such a manner as to obliterate the lumen of the appendix.

Microscopical examination showed a typical lymphosarcoma involving all the coats of the appendix, extending into the meso-appendix, and infiltrating the cecum. The neoplastic growth showed the usual signs of an acute suppurative infiltration, as did those portions of the appendix not involved in the tumor process.

Case reports of so-called malignant tumors of the appendix, cancroids or carcinomata as they are alternately termed, are now far from infrequent in the literature, but as far as a rather thorough search of it has shown, this is the first case of a lymphosarcoma. Another point of interest in this case is the age of the patient. The question of course arises as to the primary nature of the tumor. That may be answered by the statement that at operation no evident tumor process was found in the abdomen, and that ten months have elapsed since the operation with the patient still alive and apparently healthy. If the appendix tumor had been metastatic, it is more than probable that by this time other metastatic growths, or another possible primary growth, would have been discovered.

The third case is one of myositis ossificans with the history in brief that a male Italian had received a blow on the thigh muscles in the course of a quarrel. Eleven months after this blow he noticed a hard mass at the site of the previous injury which gradually increased in size, and which interfered with motion. At operation this mass was found embedded in the extensor muscles, unattached to either bone or fascia. The gross specimen consisted of a mass approximately 8 cm. in diameter and roughly circular in shape. Section through it showed numerous bony particles and a very fibrous tissue holding these fragments together. Microscopically the tissue consisted of muscle more or less degenerated and replaced by a dense hyaline connective tissue in which there were numerous islands of typical bone and cartilage without evidence of malignant degeneration.

This type of muscle degeneration is rather infrequent, a possible explanation in this instance being as follows: The initial blow caused an extensive hematoma, which in turn became organized, some of the fibroblastic elements becoming differentiated into bone and cartilage. In experiments aiming to induce cancer formation in the rat's liver by irritation, we have on two occasions seen such transformation. The livers were injured by repeated punctures with a cautery point, and in the connective tissue surrounding the burned area in one instance typical cartilage developed, while in the second instance both cartilage and bone were found upon microscopical examination. Repetition of the experiments with the idea of intentionally causing such metaplasia was unsuccessful.

The fourth case, one of primary carcinoma of the Fallopian tube, has the following history: A female, aged 45, came to the hospital complaining of the usual symptoms of diseased adnexæ. Upon operation what was thought to be a double pyosalpinx with dense adhesions to the uterus, was found, and a panhysterectomy was performed. The gross specimen consisted of a uterus, Fallopian tubes, and ovaries. The tubes were tightly adherent to the uterus and the ovaries were buried in the adhesions. Both Fallopian tubes were evidently extremely cystic. On section the uterus showed no gross changes; both ovaries were fibrous and showed cystic degeneration; the left tube contained 25 c.c. of a straw-colored fluid and had a smooth wall. The right tube contained about the same amount of a bloody fluid and showed an inner wall, rough and papillary in character. Microscopical examination of the uterus showed no malignant change, and the same was true of the left tube and ovary. The right tube showed a papillary new growth composed of columnar epithelial cells, many of which showed mitotic figures. The new growth invaded the muscular walls of the tube to a considerable depth, and directly beneath the capsule of the right ovary there were a few metastatic deposits of microscopic size.

Discussion:

Dr. Moschcowitz: In a study of many instances of ossificans, myositis ossificans is practically the only one in which pure bone is found without any evidence of calcification. In practically all other instances calcification is associated with ossification, with all the histological evidences of the calcification preceding the ossification. As I believe I have shown, calcification occurs in only dead or inert tissues eventually by a process in which angiogenesis plays a very large rôle. This area of calcification becomes ossified, in a manner analogous to normal ossification centers. Apparently this eccentric ossification rarely becomes complete because we nearly always find a zone of calcification surrounding the center of ossification. In myositis ossificans no area of calcification is ever visible; I believe therefore that in myositis ossificans the ossification does not result from the above method, but that in all probability the trauma of periosteum is the active factor.

Dr. Ewing: I should like to ask if the exact origin of the bone was determined in this case. I think that one point our chairman makes is a well taken observation, but I do not think that myositis ossificans is the sole lesion in the body where bone formation is not preceded by calcification. I think in the eye where bone often forms it is not infrequently without any preliminary calcification.

Dr. Larkin: During the last year I observed a case of myositis ossificans on one of my hunting trips in the Adirondacks. There was a wood chopper who had had repeated trauma to his arms, in the calves of his legs, and to the trapezius muscle. He had a number of knobs scattered over these regions. I removed one of these from his biceps muscle. It was very hard and entirely calcified. The most prominent thing on microscopic examination was calcification, but there was also true bone formation. In one of the athletic societies in New York there is an athlete who had myositis ossificans—so much so that he is now almost incapacitated for ordinary duties. Exhaustion of muscle in the tremendous efforts which he has made has brought about this condition in various parts of the body, and the sections which have been removed from time to time show true bone, but always in connection with calcifying processes preceding the true formation of bone. Here are two instances: one caused by repeated trauma and the other by possible muscle exhaustion.

Dr. Rohdenburg: The bone development arose apparently in degenerated muscle fibers. Some years ago in a series of experiments in which repeated puncture of the rat's liver with a cautery point was done, bone and cartilage formation occurred in two instances, but when we repeated the experiments with the intention of inducing the metaplasia, we were unsuccessful.

Dr. Ewing: I should like to ask that Dr. Rohdenburg publish a photograph of the carcinoma of the Fallopian tube, because it is one of the earliest cases I have seen. This tumor is not usually seen except in the more advanced cases.

A CASE OF VON JAKSCH'S ANEMIA OCCURRING IN A CHILD 5½ MONTHS OLD

WILLIAM C. THRO, M.D.

(From the Department of Clinical Pathology, Cornell Medical College, New York City)

In 1889 Von Jaksch described a severe anemia occurring in children. The blood of the patients which he reported had a very low total red cell count with degenerated and nucleated red blood corpuscles. The total white blood cell count was increased. Since that time a number of cases varying much in type have been reported as cases of Von Jaksch's anemia or as anemia infantum pseudoleukemia.

It is probable that in the future the cases ordinarily placed in this group will be divided into a number of different types. As one reads the reports of the cases in the literature one comes to the conclusion that some of the blood counts bear a remarkable likeness to idiopathic pernicious anemia, so-called, while others cannot easily be differentiated from chronic myelogenic leukemia of the myelocytic type, and still others resemble lymphatic leukemia. Out of the seven cases that have been counted in our laboratory since 1903, which have been studied by myself, most of them are indistinguishable from chronic spleno-myelogenous leukemia. On the other hand the case which I am now reporting is more nearly like the pernicious anemia type. The classification of blood diseases, in fact, of any pathological condition, is in a very confusing state, and I will dwell no longer upon it.

A matter of great importance, however, is the etiology of these conditions. It is possible that these severe changes in the spleen, bone marrow and liver may be brought about by some toxic infectious agent. Another factor to take into consideration is that the blood-forming organs of infants are in an unstable state and are more easily incited to abnormal function. Rickets is supposed to accompany this condition more than any other clinical manifestation, in fact the clinician usually makes a diagnosis of rickets in such cases. Malaria, syphilis, tuberculosis, gastro-enteritis and other infections have been considered as etiological factors. The etiology of Von Jaksch's anemia is also one of the questions yet to be solved by medical investigators.

The case in which I am interested was sent to the laboratory for a blood examination on December 28, 1918. The clinical diagnosis by several physicians was sarcoma of the kidneys, but other physicians thought the mass in the left side of the abdomen was the spleen. On looking at the blood smear it seemed to me that the patient must have the so-called Von Jaksch's anemia, and at the autopsy this was verified, since the enlarged mass proved to be the spleen. The mother stated that the mass in the left abdomen of the baby was found by a physician when the child was three months old, as at that time she had consulted a physician because the child was constantly crying. On calling up the physician he stated that he had made a diagnosis of splenic anemia.

When the child entered the Cornell Dispensary the weight at five months was thirteen pounds and four ounces, and in a month he lost one pound. At six months of age the weight was twelve pounds and two ounces. He appeared very bright and alert. The skin was pale, with just the faintest tinge of yellow. There were no signs of rickets. The mass in the left side of the abdomen extended down about three inches below the costal margin and a distinct notch was easily palpated.

The blood count at this time was: Hemoglobin 15 per cent. Sahli, red blood cells 1,100,000, color index 1.3, white blood cells 28,000.

Second blood count January 16, 1919. Child born July 4, 1918: Hemoglobin 15 per cent. Sahli, red blood cells 1,428,000, color index 1 +, white blood cells 39,000, after subtracting nucleated reds.

Red Cells

Anisocytosis, very marked.
Poikilocytosis, very marked.
Polychromatophilia, marked.
Granular basophilia, slight.
Normoblasts 321.
Megaloblasts 6.

Differential Count

	Per Cent.
Polynuclear leucocytes	34
Transitionals	24
Lymphocytes	23
Large mononuclears	9
Eosinophiles	1
Mast cells	1
Myelocytes	2
Leucoblasts	4
Turk's stimulation form	2
	100

Dividing nucleated reds and Jolly bodies present.

Two examinations of the urine showed nothing abnormal, except a trace of albumin. Blood and bile pigments were absent. The mother's Wassermann test was negative.

The child was sent to the General Memorial Hospital for treatment with radium, which was used only once. Several days after this it died of pneumonia and permission was given to do a partial autopsy through the persuasion of Dr. Mulcahy. The mass in the left abdomen proved to be the spleen which weighed 120 grams and measured 11 by 5.5 centimeters. The capsule was smooth, thin and glistening. Seen through the capsule the organ presented a diffuse reddish-purple appearance. The surface of the organ presented numerous pinpoint-sized, capsular stipplings. On section the organ cut readily. The substance was abundant and deep purple-red in color. The Malpighian corpuscles could not be seen. The cut end of the vessels in the splenic substance was not noticeably thickened.

Examination of the microscopical section showed that the capsule was about normal in thickness. The characteristic appearance given by the Malpighian corpuscles was absent since they were not distinguishable. There was an increase in the connective tissue stroma. Throughout the section there were foci of rather large cells, some of them with pycnotic nuclei and very reddish staining cytoplasm, probably nucleated red cells. The other cells had large vesicular nuclei and these did not show enough histological structure (because of the autolysis which had taken place) to be identified with certainty. They may be either myelocytes or myeloblasts. These are probably centers of myeloidization. Surrounding each focus was an area which was somewhat devoid of cells. The spleen probably belongs in the third group as classified by Dr. Stillman.

The left kidney was normal in size and position. The liver was pale and projected 32 cm. below the ribs on the right nipple line and 25 mm. below the costal margin in the midline. Permission to go any farther with the autopsy was not obtained.

Little can be written as to the treatment of these cases. Some of the patients recovered spontaneously. Stillman (1) reported cases from whom the spleens were removed and of these two recovered. Dr. W. S. Stone, of the General Memorial Hospital, wrote me that patients treated with light applications of radium were temporarily improved at least.

I wish to express my thanks to Dr. Thomas A. Mulcahy, through whose efforts we were enabled to study this case.

Bibliography

1. *Am. Jour. Med. Sc.*, 1917, cliii, 218.

Discussion:

Dr. Ewing: I think it would be interesting if one could find in the spleen some source of the enormous number of nucleated red cells found in the circulation, but I cannot see that the cells in the spleen are hemoglobin-holding. Of course some nucleated red cells contain very little hemoglobin, so that, considering the rather poor fixation of the spleen, it is possible that many hemoglobin-holding cells would not be recognizable on staining. But on the whole I think if the spleen had contained any considerable number of nucleated reds they could have been recognized. This leaves practically only the bone marrow as the source. The liver is noted as being enlarged. The only case I have seen at autopsy of uncomplicated von Jaksch anemia was one I reported years ago, and in that the capillaries of the liver were the seat of numerous foci of what Dr. Thro would call leukoblasts. I do not feel that without new data I can engage in any speculation regarding the nature of von Jaksch anemia, but still, perhaps it is safe to refer to an opinion formed many years ago to the effect that von Jaksch anemia is probably an exhibition of the very unstable regenerative efforts of the blood forming organs in infants, and that the enormous increase in the nucleated red cells is to be interpreted as similar to that seen in adults on a small scale in primary anemia. I do not see that there has been any new evidence brought forward since that time which would confirm or dispose of that theory.

Dr. Moschcowitz: May I ask from what the child died?

Dr. Thro: The doctor who took care of it in the last days made the diagnosis of bronchitis and pneumonia.

Dr. Moschcowitz: The question of the prognosis of von Jaksch's anemia has always interested me. I have no idea as to how many of these cases recover, and how many die. This is another instance of an uncommon chronic disease in which we see only the intermediary stage, never the beginning, and only very rarely the end.

VAQUEZ'S DISEASE

DOUGLAS SYMMERS, M.D.
(*Director of Laboratories, Bellevue and Allied Hospitals*)

AND

E. APPELBAUM, M.D.
Interne, Bellevue Hospital

(*From the Pathological Laboratories of Bellevue Hospital*)

Erythremia, polycythemia vera, or Vaquez's disease, is characterized by persistent increase in the number of red cells in the circulating blood, by splenomegaly and, as a rule, by cyanosis. The observation of Vaquez, confirmed by Weber and others, that the bone marrow is the seat of increased erythrogenesis affords, it would seem, the most plausible explanation of the process as a whole. In most cases of chronic cyanotic polycythemia the augmented activity of the erythroblastic tissues of the bone marrow is so well equilibrated that, for the greater part, only mature red cells are thrown into the circulation, a few normoblasts and a casual megaloblast being encountered on occasions, fairly large showers of megaloblasts having been observed in at least one case. These facts suggest that the cause of the disease is to be sought in the bone marrow, the reaction of whose hematogenetic tissues, more especially the erythroblastic centers, is of much the same character as that of the lymph nodes in chronic lymphatic leukemia and of the myeloblastic bone marrow in myelogenous leukemia, in other words, that chronic cyanotic polycythemia is the red cell equivalent of the leukemias, the preponderance of circulating erythrocytes being paralleled by the lymphocytosis of lymphatic leukemia and by the myelocytosis of myelogenous leukemia. In both varieties of leukemia, of course, the spleen is always enlarged. In myelogenous leukemia the enlargement is due practically exclusively to the infiltration of myelocytes from the hyperplastic bone marrow. In lymphatic leukemia the process of lymphocytic infiltration of the spleen, while caused in great measure by cells brought from the enlarged lymph nodes, is contributed to by proliferation of the lymphoid follicles normally resident in the spleen itself. In chronic cyanotic polycythemia enlargement of the spleen is occasioned solely by erythrocytic infiltration, the organ acting as a reservoir.

In the greater number of all cases of genuine Vaquez's disease simple enlargement of the spleen is present, the organ sometimes attaining a weight of 2,000 gm. or more, reaching from a few fingers' breadths below the costal slope to points within the pelvis. Microscopically this variety of splenic enlargement is marked by congestion of an extreme degree, and the process is apparently best interpreted as an effort on the part of the spleen to withdraw and destroy superfluous red corpuscles, and thus mechanically to relieve the vascular embarrassment occasioned by massive increase in the total volume of cells. The cyanosis may equally well be explained on mechanical grounds, the over-production of red cells by the bone marrow, continued without appreciable interruption, eventuating in capillary engorgement throughout the body, the result being first visualized in those vessels which are most frequently subject to mutations in temperature and posture and in those whose vaso-motor control is least stable, including, therefore, the vessels of the face, of the tongue and pharynx, and of the extremities, notably the hands and, later, throughout the skin. Whether, as has been suggested by some, the mechanical effects of increased erythrogenesis are reënforced by diminished destructibility of red cells, is problematical, both Almoth Wright and Saundby having been unable to determine any change in the hemolytic index. The older conception that the disturbances in the bone marrow are secondary and passive phenomena is largely gratuitous, inviting assent without offering proof. Moreover, since there are authentic cases of polycythemia with splenomegaly but without cyanosis it would appear that, to a certain point, the spleen is mechanically capable of taking care of the excess of red blood cells, but that beyond this point its receptive capacities are transcended, and the excess of red blood corpuscles is distributed elsewhere, and polycythemia is then externalized by distension of the blood vessels of the face, mouth, throat and extremities. That the spleen acts as a reservoir for excess red cells is apparent in physiological circumstances and is shown by increase in the size of the organ during digestion. In short, the functions of the adult spleen appear to be largely mechanical. Although there are circumstances in which the spleen in adult life displays a tendency to revert to its embryonal function as a blood-forming organ to compensate for deficiencies in the bone marrow, its attempts in this direction are nevertheless feeble. On the other hand, the tissues of the spleen lend themselves to the arrest of foreign bodies, such as bacteria and other parasites, including the plasmodia of malaria, trypanosomes, and the like, together with living cells which are discharged from their normal abode and thrown into the circulation as emboli, among them, myelocytes in myelogenous leukemia and myeloplaques in Hodgkin's disease.

In view of these facts it is not surprising to find that most of the massive splenomegalies are secondary to disturbances elsewhere. Recognition of this point is of practical value. For example, in Vaquez's disease the splenic enlargement, as already indicated, probably is mechanical in nature and consequently is an aid rather than a hindrance. Splenectomy, therefore, is contra-indicated, not alone for the reason suggested, but also because experience has shown that in those instances where the patient survives operation no improvement is to be observed and, moreover, because operation in this class of patients is attended by high mortality due, as a rule, to post-operative capillary oozing, death occurring within thirty-six or forty-eight hours. Even in those cases of Vaquez's disease where there are clinical reasons for the belief that the spleen is the seat of localized tuberculosis, the indications for splenectomy are questionable since, in these circumstances, infection by the tubercle bacillus is probably secondary, in many cases at least, to the polycythemia and splenomegaly. On the contrary, splenectomy in cases of uncomplicated primary tuberculosis of the spleen is another story, the operation yielding highly favorable results.

A case of Vaquez's disease was recently observed at Bellevue Hospital. The massive spleen will be shown to you to-night. We had hoped to submit microscopical preparations, but an accident prevented.

The patient, a man, aged 54, was admitted to Bellevue Hospital with the statement that, for ten or twelve years past, he had been "blue in the face" or, in warm weather, that his face became reddish in color. During the same length of time he suffered from periodic attacks of headache and dizziness. On admission to Bellevue Hospital he stated that, while crossing the street, he was seized by an attack of dizziness and fell against a pillar of the elevated railway. He was received at the hospital in a semi-conscious state. Physical examination showed a striking bluish red discoloration of the face, upper chest, arms, hands and feet and of the mucosa of the mouth and pharynx. The veins of the anterior abdominal wall were dilated and the spleen was felt as low as the level of the umbilicus. There were three lacerated wounds of the scalp from which blood oozed continuously, and on three occasions the wounds bled profusely. Ophthalmoscopic examination showed engorgement of the retinal veins. The blood pressure was systolic 120, diastolic 75. The Wassermann reaction was negative on two occasions. Chemical analysis of the blood showed:

	Mg. per 100 c.c. of blood	Normal
Sugar	181	50 to 110
N. P. N.	39	25 to 40
Urea	17	10 to 20
Uric acid	6.4	1 to 3
Creatinine	4	0.1 to 1

The coagulation time was six to seven minutes.

The blood count on admission was: Red cells 9,000,000, white cells 8,000, hemoglobin 110 per cent. Twelve days later the red cells numbered 8,000,000, white cells 8,000 and hemoglobin 115 per cent.

Splenectomy was done a month after admission. Upon removal the spleen weighed 1,540 gm. Death occurred two days after operation and was due to capillary oozing.

At autopsy no changes worthy of note were found other than extensive hemorrhage into the abdomen, generalized congestion of the viscera, and intense redness of the bone marrow throughout the body, the marrow of the ribs, vertebræ, femora and skull having been the most carefully examined. Microscopic investigation was made of all the viscera. Except for intense congestion, no particular changes were found. Smears from the bone marrow showed the presence of excessive numbers of red cells together with large numbers of white forms of the type of lymphocytes. Nucleated red cells were not found although sought.

The presence in the bone marrow of considerable numbers of white cells of the lymphocytic type does not appear to be peculiar to Vaquez's disease, since one of us only recently has observed similar, if not identical, changes in the bone marrow of a syphilitic but non-leukemic individual whose spleen weighed over 3,000 gm.

Discussion:

Dr. Moschcowitz: These cases clinically are really not so uncommon. In my short career I can safely say that I have seen a dozen; what interests me especially is what happens to these patients. We are confronted with this problem in a great many chronic diseases of unknown origin: we see the middle stage, but we never see the beginning and we only rarely see the end. I do not recall ever having seen an autopsy of a person who died of Vaquez's disease.

Dr. Schultze: I saw a case some years ago which was under the treatment of Dr. I. Adler. There was an excess of red cells and a marked excess of blood platelets. The spleen was much enlarged with tuberculosis. There were secondary tuberculous deposits in some of the organs of the body. If I remember correctly the bone marrow showed very little change. There was evidently a primary tuberculosis of the spleen and polycythemia.

Dr. Moschcowitz: Clinically they have a rather characteristic appearance. The cyanosis is not the type seen in cardiac or pulmonary disturbances. These patients have a ruddy color. Sometimes it is very hard to determine what is a polycythemia and what is not. Frequently we find patients with a large, hard, palpable spleen, and with a blood count that is only about four and a half to five millions, and it is a rather difficult problem to know into which category such a patient should be placed.

Dr. Ewing: I should like to say a few words about the treatment. For three years past we have been treating at the Memorial Hospital a case of Vaquez's disease by applying over the spleen, sternum, and spine large amounts of radium. The results in the first year were quite striking; during that year the patient had more relief than she had received from any other treatment. During the second year her health was not quite so good, but still tolerable; in the third year the symptoms seemed to be re-asserting themselves. Nevertheless, I think that in the absence of any very satisfactory method of treatment for these cases, the method of radium application is worth trying.

Dr. Moschcowitz: The conventional method of treatment is repeated venesections with transfusions of salt solution.

Dr. Larkin: In looking the specimen over I noticed several catgut sutures at the hilus of the spleen which attracted my attention to what the doctor said about the abdomen being filled with blood at autopsy. It came to me that the condition of blood in the abdomen might have come about at the time they were attempting to remove the spleen at operation. I always dislike having a man's name attached to a condition like this, which, it seems to me, is not a disease. I think it is entirely a mechanical condition, and I think those of us who have had the opportunity of observing the individuals about 55 years of age who come to the morgue do not infrequently find spleens of just this character in persons who have been chronically stimulated for years. They show conditions which are those of chronic hyperplasia in the spleen, and also show chronic changes in the circulatory apparatus and changes in the bone marrow. I do not think that we have paid enough attention to the individuals who have had more or less chronic disturbances in the circulatory apparatus. I think that the condition here is not a true disease, but is simply a mechanical disturbance which has gone on for some years. I was rather surprised also in hearing the question of primary tuberculosis of the spleen raised. I have yet to find out where the thing shows such a condition, so that I should like to go on record against such an explanation, and to reiterate that after all this thing represents nothing but a mechanical interference which manifests itself in a productive inflammatory condition in the spleen.

PULMONARY LESIONS OF INFLUENZA PNEUMONIA, AND A METHOD OF MUSEUM PREPARATION

JAMES EWING, M.D.

My object in presenting these slides this evening is to demonstrate a method of preparation of lungs of influenza or other pulmonary diseases for gross anatomical study, and for permanent preservation in a museum. We might ask perhaps what is the use of making a separate topic of a matter of this sort. I found this summer at the Army Medical Museum at Washington that there was very great need for information on this subject, and it was only after a considerable and harrassing experience that we were able to obtain any satisfactory gross material, that is, which demonstrated the lesions of influenza in a fully adequate manner. It was only after a number of trials and experiments that we adopted a method which will be demonstrated in these slides. That method consists briefly in attempting to demonstrate fully the lesions in both lungs, because without the demonstration of the lesions in both lungs one might get a very erroneous idea of the nature of the pulmonary lesion in influenza. I had many consultations with Dr. MacCallum, and it is owing to his energy that we have any material at all from the epidemic of so-called post-measles pneumonia in 1917. Knowing that the lesion is bilateral, and may vary considerably in both lungs, we agreed that we must have both of them for study. Finally, at St. Elizabeth's Hospital, we perfected a method which is easy to describe, but not so easily applied. The plan is to lay the lungs, removed together, on their anterior surfaces and to cut both lungs down the bronchial tree. With a long sharp knife make a slice where the bronchial tree is running. That cuts off the posterior portion of the lung a slice about two inches thick from the apex to base. The first cut may not strike the bronchial tree throughout its entire length, but one can make another cut which will continue the section to the finest ramifications of the bronchial tree, and when this is done, it gives a striking picture (Fig. 1). There were

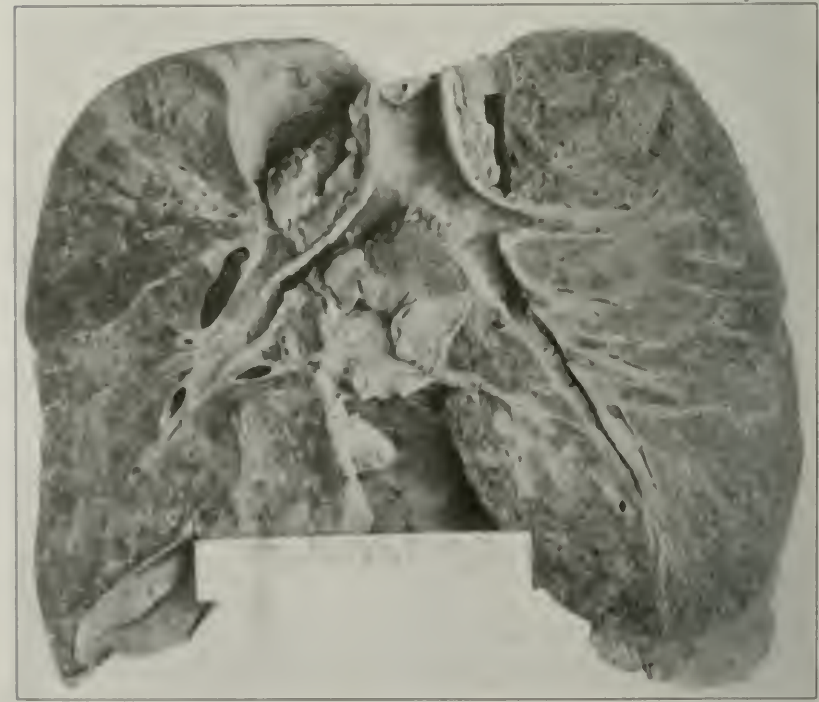


FIG. 1. A characteristic type of bronchopneumonia following influenza.

several results of the study of lungs sectioned in this way which I think would not have been secured by cutting the lungs in a haphazard manner, as is usually done.

In studying the lungs we found what I call a critical area around the centers of the main bronchi in both lungs where as a rule secondary pneumonic processes are apt to begin. I had quite a discussion with some internists once on the question whether pneumonia began under the pleura or in the central area, and I could not answer the question. In our own museum specimens there were illustrations of both conditions. In a series of sections cut in this way through both lungs we have found in a large proportion of post-influenzal pneumonias that consolidation began in an area around the bronchial tree, which became so common that we designated it as the critical area. Another point which has been brought out, and which I think could only have been done to full satisfaction by this method of section, was that in practically all our cases the original lesion was a bronchiolitis. Sometimes a secondary and diffuse pneumonia would start all through a lobe or through several lobes, so that on inspection one could not make out a trace of the original bronchiolitis, but in a high proportion of cases one would find a tell-tale peripheral zone of fine bronchiolitis. Another matter which was emphasized only lately, and which can be demonstrated in the slides, was the characteristic condition of the lung in most cases of empyema. I had never seen it before. I have been told that Ribbert described it, and also have been told by members of the Empyema Commission that they had concluded that a peculiar type of lesion must exist in the lung in cases of empyema. Here a streptococcus infection spreads through the lymphatics of the bronchioles and of the septa and thus reaches the pleura. It passes rapidly through these lymphatic channels, and distends them with pus to a very noticeable extent. In the earlier stages of this type of lung one finds the septa clearly marked out in a characteristic mosaic. This lesion might almost be spoken of as an abscess, but it is not a true abscess. There is no liquefaction, but the lymphatics are very widely distended with exudate. This lesion, occurring in one or both lungs, can be satisfactorily traced to the root of the lung only in sections made in this particular manner.

I do not expect this evening to give a complete demonstration of the pulmonary lesions in influenza, but hope only to show the main features, and I trust that the slides will impress on the members of the society how important it is for pathologists to take pains in preserving specimens.

LANTERN SLIDE DEMONSTRATION

The slides were arranged in the following groups:

1. Diffuse bilateral hemorrhagic pneumonias. Bronchiolitis obscured by blood. Cases from height of epidemic.
2. Fine bronchiolitis all over both lungs, which are very red, but show little exudate.
3. Lobular or diffuse pneumonias obliterating the bronchiolitis except at periphery.
4. Increasing prominence of bronchiolitis and bronchopneumonia, with or without patchy pneumonias.
5. Necrotic bronchopneumonias resembling tubercle.
6. Lungs in empyema.
7. Comparison of lungs of 1918 with those of 1917.

One of the conclusions resulting from a comparison of the lesions of 1917 and 1918 caused much opposition, and of course it was based only upon such evidence as pathologico-anatomical data. But I think that the fact that from the gross anatomical standpoint the lungs of the so-called post-measles pneumonia of 1917 correspond in even minute detail, with the lesions that have been found in the epidemic of post-influenza pneumonia, is suggestive that these pneumonias are essentially the same. This fact hardly permits one to state such a conclusion as final The nature of these diseases is to be decided finally by bacteriological data, but since the bacteriologists have not as yet arrived at any conclusion in the matter, it seems to me it would be wise not to dismiss entirely the evidence which may be obtained from the gross anatomical study of the lungs. It may also be noted that in 1917 influenza bacilli were frequently found and reported, but camp bacteriologists considered them of no importance. This was not noted until the reports were reëxamined in 1918. I think it is desirable to emphasize the wisdom and necessity of making every effort to preserve the characteristic specimens of these lesions. The question arises what is the relation of post-measles pneumonia to pure measles. It is not easy to answer this question. Few if any museums possess a well-preserved set of lungs in a case of measles. I think it would be very important evidence if we could point out that this or that particular specimen belongs to measles. It has been my hope that we could get a group of selected specimens which would show every variation in the type of these influenza and measles pneumonias which might settle some of these questions from the gross anatomical standpoint and form a basis for the study of the etiology of these diseases on the bacteriological side.

Discussion:

Dr. Cole: I will not discuss this paper more than to express my appreciation of the splendid work Dr. Ewing has done in studying the pathological lesions in these cases of pneumonia. It is not only in bronchopneumonia that our knowledge is lacking of the exact pathological lesion. We have been interested for a long time, more from the bacteriological standpoint, in lobar pneumonia, and I have been struck with the lack of exact knowledge of the lesions, and I think a careful study of the lungs and the lesions produced in lobar pneumonia would give us a good deal of valuable information concerning the nature of this disease. In regard to the lungs described to-night by Dr. Ewing, one is struck by the great variety in the lesions. It is quite true, as Dr. Ewing states, that certain of these lungs show lesions which are like those we saw in 1917 and again in 1918, before the present epidemic of influenza occurred. I studied the pneumonia occurring at San Antonio in the winter of 1917–18. It is true we found the influenza bacillus in the lungs in many of the cases, but we did not lay stress upon this. Most of the cases of pneumonia with peculiar lesions occurred in association with measles, but we pointed out that similar cases occurred without measles. If the disease we were studying was influenza, it is difficult to understand why it should have taken on the remarkable epidemic character which it has exhibited this winter. I do not know what influenza is, except that it is an acute respiratory disease occurring in remarkable epidemic form and usually associated with leucopenia. In going over the records of our cases during the epidemic I find all clinical varieties of respiratory disease which we had to label "influenza," from coryza to the most severe bronchopneumonia, and it is impossible to say from the clinical features alone that "this is influenza" and "this is not influenza." One point I should like to inquire about is the peribronchial infiltration, which was such a marked feature in the measles cases. Many of these cases associated with empyema showed also a severe lymphangitis with dilatation of the lymph vessels running out to the periphery. Some of the cases showed marked bloody exudate and extreme edema of the lungs, as have been seen in the present epidemic. Such cases are still occurring. Only the other day we had such a case and the same day another case with staphylococcus infection, the lung showing numerous abscesses. In both of these cases influenza bacilli were isolated from the lung, and it seems that both cases must be considered as associated with the epidemic through which we have just passed. None of the lung lesions so far described seem to me definite enough to permit us to consider them specific. With the clinical picture so variable and with no well established etiology I still have difficulty in defining influenza.

Dr. Manges: Does Dr. Ewing adhere to the classification that Dr. MacCallum has so recently introduced, that is, that the influenza bacillus gives a typical picture, as does the streptococcus and the staphylococcus? I judge from the pictures this evening that they are quite uniform types. I should like to ask Dr. Cole whether in the measles cases there was a typical infiltration of the lungs. I think we have to add to the leucopenia a slow pulse and a slow respiration, which we must include in the medical picture of influenza. I think those of us clinicians who are here to-night can only appreciate deeply what Dr. Ewing has given us in his presentation. It emphasizes more than ever the extension of the disease from the so-called critical area. Another point is that of the dilated bronchi in relation to empyema cases, and that is one which is being overlooked constantly, and which would also explain the gravity of the case in empyema, which is also often overlooked.

Dr. Williams: The evidence that Dr. Ewing gives of post-measles lungs being similar to the so-called influenza lungs adds somewhat to the evidence in favor of the influenza bacillus being a secondary invader in the pandemic.

Dr. Moschcowitz: Dr. Ewing's description of the erysipelas of the lung interested me especially. My brother, Major A. V. Moschcowitz, who is a member of the Empyema Commission, tells me that invariably in the cases of empyema there is a subpleural abscess that has ruptured. I would like to ask Dr. Ewing if he has found that to be the case.

Dr. Ewing: I should like to emphasize the fact that while I am impressing the importance of pathological anatomy, I do not wish to overemphasize it. It happened to be my job to do something in this field, and I went to it with the usual energy which we would all display in such a case. I have not said anything about the histology of these lesions, although I can assure you it is just as variable as the gross anatomy, but in general I think there is one central tendency which is quite striking. Throughout the entire series of post-measles and post-influenza pneumonias, usually complicated by streptococcus infection, whenever there is a bloody exudate and a severe distortion of the walls of the bronchioles, there is a certain tendency toward organization. In a great many of the earlier cases organization was not found, but it was extremely common in the later specimens.

As to the bacteriology of these lungs, quite a corps of assistants worked in attempting to trace the bacteria demonstrable in sections of the lungs. It is a very laborious process, and one about which you do not see very much said in the reports of the laboratories. I think in general there is a very wide variation in what one will find using Gram's stain, carbol-fuchsin, etc., in studying these lungs. Some lungs show no bacteria, that is, in the portions which come in the section. Others show a tremendous overgrowth of staphylococcus, pneumococcus or streptococcus. There are all variations. In not a few one can find a few Gram-negatives, along with an overgrowth of Gram-positives, leading to the conclusion that it is the Gram-negative organisms which sweep over first, then disappear, and are replaced by the Gram-positive types.

In regard to Dr. Cole's question of the round celled and perivascular infiltration that is present, I understand that every time one says "bronchopneumonia" he means a lesion affecting the walls of the bronchioles and the walls of the air vesicles immediately surrounding them, and that this infiltration is essentially an interstitial process. The infiltration consists of round cells, lymphocytes, and plasma cells. The process is essentially a productive inflammation. I think Delafield interpreted it correctly. In addition to the interstitial inflammation, there is nearly always an acute purulent catarrhal exudate into the lumina of the bronchioles, and that is present in practically every one of the lungs studied. The point Dr. Cole makes as to the existence of an essential and specific anatomical lesion in influenza seems to me is the essential point in the whole discussion. If we could establish that there is an essential lesion in influenza-pneumonia then we could go a long way toward determining the relation of these different types and form the basis for the bacteriological study. Now there appear to be sufficient data on which to construct a specific lesion for the lungs in influenza. I think it consists of a purulent bronchiolitis with bronchopneumonia limited to the tissue immediately around the bronchioles, uniform, and involving the finest ramifications of the bronchioles. That I think is pretty nearly a specific thing from the anatomical standpoint. We may not be able to recognize the condition clinically. But its bacteriology has not been settled yet, although from some sources it is said that if you get an early lesion you will find the influenza bacillus in practically pure culture in the pus from the bronchioles. I think all this points to the conclusion that the lesion which I have described is the specific thing in what you call influenza. The fact that this lesion often occurs in measles does not indicate that measles and influenza are the same disease, but merely suggests that such post-measles pneumonias are influenza grafted on measles. In regard to abscesses in the lungs, I heard that statement from several sources, and can only partly confirm it. Subpleural pus is present in practically all cases of empyema, but it is a lesion which I would not call an abscess at all. What you see is a phlegmonous lymphangitis, spreading so widely as to resemble a phlegmonous erysipelas, and not an abscess. The lung tissue is not destroyed; it is widely spread apart by pus and edema, but there is no destruction of the tissue.

THE RELATIONSHIP OF B. INFLUENZÆ TO CLINICAL INFLUENZA

F. M. HUNTOON, M.D., AND S. HANNUM

(*From the Mulford Biological Laboratories, Glenolden, Pa.*)

Owing to the constant finding of influenza bacilli in cases of clinical influenza, both during life and at autopsy, and to the fact that the initial symptoms of the disease are those of an acute toxemia, the following investigations were undertaken in an attempt to determine the relationship of the *B. influenzæ* to the disease.

The experimental work was divided into four sections.

1. Toxic factors in *B. influenzæ* infections.
2. Serological relationships of *B. influenzæ* strains.
3. Pathology of the lesions caused in experimental animals by the *B. influenzæ* and its products.
4. The influence of the *B. influenzæ* and its products on secondary invasions of the lung.

Owing to a preliminary failure to demonstrate a soluble toxin in growths of this organism, we were led to attack the problem of an endotoxic factor. Ten strains of influenza bacilli giving fair amounts of growth, dried in vacuo, ground up with salt and extracted, were employed. This material tested for its killing power on white mice gave the following result:

TABLE I

Toxicity of Salt Extract

(Ten strains of influenza bacilli dried)

Extract c.c.	Mice			
1.0	D18	D18	D24	
0.5	D18	D18	D18	
0.25	D24	D72	D18	
0.1	Liv.	D46	D48	Injections in the peritoneum
0.05	Liv.	Liv.	D48	
0.025	Liv.	Liv.	Liv.	

If such a reaction as shown in the table is specific, one should be able to demonstrate protection with an immune serum.

TABLE II

Protection tests against influenza toxic extract, employing a serum from a horse immunized against the same ten strains (live organisms)

Extract, c.c.	Serum	Mice		
1.0	0	D18	D24	
0.5	0	D18	D24	
0.25	0	D24	D72	
0.1	0	Liv.	D18	
	c.c.			
1.0	0.1	D24	D24	
0.5	0.1	Liv.	D36	
0.25	0.1	Liv.	D72	Serum given simultaneously
0.1	0.1	Liv.	Liv.	
0.5	0.5	Liv.	Liv.	

This table shows some degree of protection, but not to a marked degree.

A second series was run in which the serum and extract were left in contact 30 minutes at room temperature before injection, as shown in Table III.

TABLE III

Extract, C.c.	Control	Mice	Protection Test		
			Extract, C.c.	Serum, C.c.	Mice
1.0	0	D24	1.0	0.1	Liv.
0.5	0	D24	0.5	0.1	Liv.
0.25	0	D24	0.1	0.1	Liv.
0.1	0	D24			

This shows protection against at least 10 M.L.D.

It was further found that when the streptococcus hemolyticus was grown in symbiosis with influenza bacilli in broth that a similar toxin was produced which is protected against by the same immune serum.

The streptococcus under these conditions seems to have a disintegrating effect upon the influenza bacilli.

TABLE IV

Strept.-Influenza Filtrate c.c.	Serum	Mice	
1.0	0	D24	D24
0.5	0	D24	D24
0.25	0	D24	D24
0.1	0	Liv.	Liv.
	Immune Serum		
1.0	0.2	Liv.	Liv.
0.5	0.2	Liv.	Liv.
0.25	0.2	Liv.	Liv.
0.1	0.2	Liv.	Liv.
	Normal Serum		
0.5	0.5	D24	D24
0.25	0.5	D48	D48
0.1	0.5	Liv.	Liv.

Control experiments with the streptococcus alone gave a toxic product, but not of the same degree, and this product was not neutralizable by the immune serum.

These tests are sufficient to show that it is possible to extract a substance from the influenza bacillus which has a killing influence upon small animals.

The pathological lesions in these animals are uniformly that of an acute congestion of the lungs with occasional hemorrhages into the alveoli and into the pleura.

While this work was in progress a report was published by J. T. Parker[1] detailing work along similar lines. She succeeded in producing in broth cultures a soluble toxic product. We have repeated this work and can confirm her results.

1. This product is of a somewhat similar nature to the salt extract endotoxic product and the two substances cross immunize.

2. *Serologic Investigations.*—We have found that the polyvalent horse serum and monovalent rabbit and guinea-pig sera show cross relationship between the various strains of influenza bacillus studied, even the strains isolated from sporadic cases before the start of the present epidemic. These relationships were shown by agglutination tests and absorption of agglutinins and cross protection tests.

---

[1] *Jour. A. M. A.*, 72, 476, 1919.

TABLE V

Protection tests against various strains of influenza bacilli, both homologous and heterologous

Serum: polyvalent horse serum 79699.

All emulsions standardized to a strength of 5,000 million to c.c.

Injections of serum and emulsion were made simultaneously into the peritoneum of white mice.

Dose Serum	Dose Emulsion, C.c.	Strains								
		117*	136*	141*	143*	144*	120	130	131	132
0	1.0	D24	D18	D24	D18	D18	D24	D18	D18	D18
0	0.5	D18	D18	Liv.	S. D18	D18	D24	D18	D18	D18
0	0.25	D18	D24	D36	D24	D24	D48	Liv.	D18	Liv.
0	0.1	D36	D48	Liv.	D24	Liv.	Liv.	Liv.	D18	Liv.
Normal c.c.										
0.5	0.5			D18	D18	D18		D18	D18	D18
Immune c.c.										
0.1	1.0	Liv.	Liv.	Liv.	Liv.	Liv.	Liv.	D18	D48	Liv.
0.1	0.5	Liv.	Liv.	Liv.	Liv.	Liv.	Liv.	Liv.	Liv.	D–

D = Dead with number hours lived.

Liv. = Recovering.

S = Sick.

TABLE VI

Absorption test to determine relationship of strains employed for immunization and others not so employed

Serum: polyvalent 79699.

Strain for absorption 143 (Hygienic Laboratory 103) heavy emulsion.

Dilution at which absorption occurred, 1:25.

Temperature at which absorption occurred, 37° C.

Time, 2 hours.

Untreated serum control

	C	50	100	200	400	800	1,600	
117	—	1	4	4	4	3	—	Immunizing strains
144	—	3	4	4	4	—	—	
132	—	—	4	4	4	4	—	Non-immunizing strains
138	—	4	4	4	4	—	—	

Absorbed Serum

117	—	—	—	—	—	—	—
144	—	3	1	—	—	—	—
132	—	—	—	—	—	—	—
138	—	—	—	—	—	—	—

* Marks homologous immunizing strains.

3. *Pathology of Experimental Influenzal Infections.*—The salt extract toxin and broth toxin and streptococcus-influenza toxin produced uniformly acute congestion of the lung with occasional hemorrhages into alveoli and pleura.

4. *The Influence of the Organisms upon Secondary Invasions.*—Injections of the influenza bacilli or its products into animals in sublethal doses predisposed these animals to infection of the lungs with other organisms, either spontaneously or artificially when the organisms were introduced into the pharynx or into other parts of the body.

CONCLUSIONS

1. That the influenza bacillus is capable of producing a toxic substance.

2. That this substance when introduced into the circulation produces congestion of the respiratory tract with hemorrhages into the alveoli.

3. That certain conditions of symbiotic growth intensify the liberation of the toxin.

4. That as an effect of the action of the poison the lungs show a predisposition to invasion by various organisms, with the production of secondary lesions.

5. That there is nothing in the serological evidence to preclude the consideration of this organism or its influence as an important factor in the disease known as clinical influenza.

Discussion:

DR. WILLIAMS: Dr. Huntoon's work is extremely interesting and important from the standpoint of the pathogenicity of the influenza bacillus, but until further corroborative serological tests show that the majority of the strains isolated during the pandemic are the same, there is very little evidence added as to the relationship of the influenza bacillus to the cause of the pandemic. We have so far tested over 160 strains of the influenza bacillus. About fifteen were isolated from autopsies; over sixty were isolated from the earlier cases at the beginning of the epidemic, others were controls, and from these 160 strains we have only four pairs. With direct agglutination, of course, we have gotten quite a good deal of crossing, but we have obtained practically no crossing after absorption.

Dr. Cole: It is extremely interesting, almost of prime importance, if Dr. Huntoon thinks he has succeeded in demonstrating a specific toxin obtained from the influenza bacillus, and I wish he would tell us a little more of the details of the method employed in producing this toxin. Bacterial toxins are not very numerous, and if he has succeeded in demonstrating a true toxin, he has made a very important addition to our knowledge of infectious disease.

Dr. Hatfield: I should like to ask Dr. Huntoon the exact source of the strains he used.

Dr. Ewing: I have had the opportunity to examine the sections. It is very difficult to demonstrate any specific feature of the lesions produced under these circumstances in such small animals. I think, however, that the extreme hyperemia and miliary hemorrhages of the so-called toxic lungs are rather striking. That raises the question whether other toxins will not do exactly the same thing. The lesions produced by the toxin plus the inhaled streptococcus are very close reproductions of some of the lesions seen in cases of human influenza.

Dr. Jobling: I should like to ask Dr. Huntoon if he used any other types of organisms, or other substances, before using the streptococci, and also, if he made any blood examinations, and if so, was there a leucopenia. While working with meningococci several years ago, I obtained toxins as strong, and in some instances, stronger, than those just described by Dr. Huntoon. We believed, however, that these were endotoxins, as we were unable to use them for the standardization of the anti-meningococcus serum.

Dr. Huntoon: In regard to the matter of growth which Dr. Cole asked about. These organisms are grown upon agar. It is half lung and half beef heart, and to it is added horses' blood in the proportion of about 2 to 3 per cent. It is placed in the autoclave for two to three minutes and then slanted and used. Concerning the question of toxin production: The material was transferred to Petri dishes and dried in vacuo over sulphuric acid. It takes about four days to dry it out. We then prepared it as I described in my presentation, by grinding it up with salt, so that we exposed the organism to concentrated salt solution, and apparently obtained the material in solution in that manner. The streptococcus-influenza toxin is plain enough, that is, just growing the streptococcus in an emulsion of the organism for 48 hours and then taking it off through a Berkefeld filter. The broth we used was plain vitamine broth. The source of the cultures was varied: strain 117 is an old strain isolated in 1917 from a case of tonsillitis. Most of the strains were isolated in Philadelphia during the epidemic there. Strains 141 and 143 we obtained from the Hygienic Laboratory. One hundred and forty is the so-called Boston strain. Another came from the Army Medical School. We felt that we had a rather wide distribution. Four were isolated in 1917 before the epidemic in this country started. You will note carefully that I do not claim causal relationship for these organisms. I do not think that the evidence is sufficient to claim any such thing, but I think that the results show that it is possible to explain the disease and not use any other organisms but those which we have found in cases of the disease. In an article by Gibson and Kent in the *British Medical Journal* for December, in discussing a filterable virus, the description of the lungs for some of their monkeys could be transferred to some of our animals.

We have used control animals with meningococcus extract, made in the same manner, and also pneumococcus extract and streptococcus extract. With none of these were we able to kill mice with doses of one cubic centimeter. We killed some of the animals and the lungs did not show anywhere near the degree of hyperemia that these influenza lungs did.

TWO UNUSUAL CASES OF MELANOCARCINOMA

H. A. MURRAY, M.D.

(From the Department of Surgery, College of Physicians and Surgeons, Columbia University, New York)

I shall present the histories and pathological specimens of two cases of malignant neoplasm of the same type, the characteristics of which are sufficiently distinct, we believe, to make the diagnosis unmistakable.

Malignant melanomas are not uncommon and we would not have considered these cases worth recording if it were not for the fact that their clinical appearance was unusual enough to puzzle a number of capable surgeons who remained ignorant of the true nature of the tumors until the pathological reports were made known. Believing that on this account they will be of some interest to the society, I offer the following cases for your consideration:

CASE I.—No. 64383. Mrs. D., housewife, aged 35 years, entered the Presbyterian Hospital on October 29, 1918, complaining of a tumor of the right lateral costal region of six years' duration.

Present Illness. The patient says that she has always had a small brown mole at the site of the present tumor. Six years ago this was tied off and later for some reason treated with cocaine, leaving a brownish speck in a small scar which spread slightly but gave no trouble until three years later. At this time the mole became irritated and broke open with some bleeding. After healing a small lump remained. Twenty-one months ago at the end of her third pregnancy, the lump again became irritated and broke open. Since that time it has grown rather rapidly in size, especially in the last two months, and there has been a persistent reddish-yellow discharge.

She complains of continuous dull pain in the tumor and frequent shooting pains radiating from the axilla around the side to the site of the mass. The pain is increased by using the right arm, which feels numb. For the past three months she has noticed swollen glands which have grown rapidly in the right armpit and right side of neck. Lately she has lost some weight and strength.

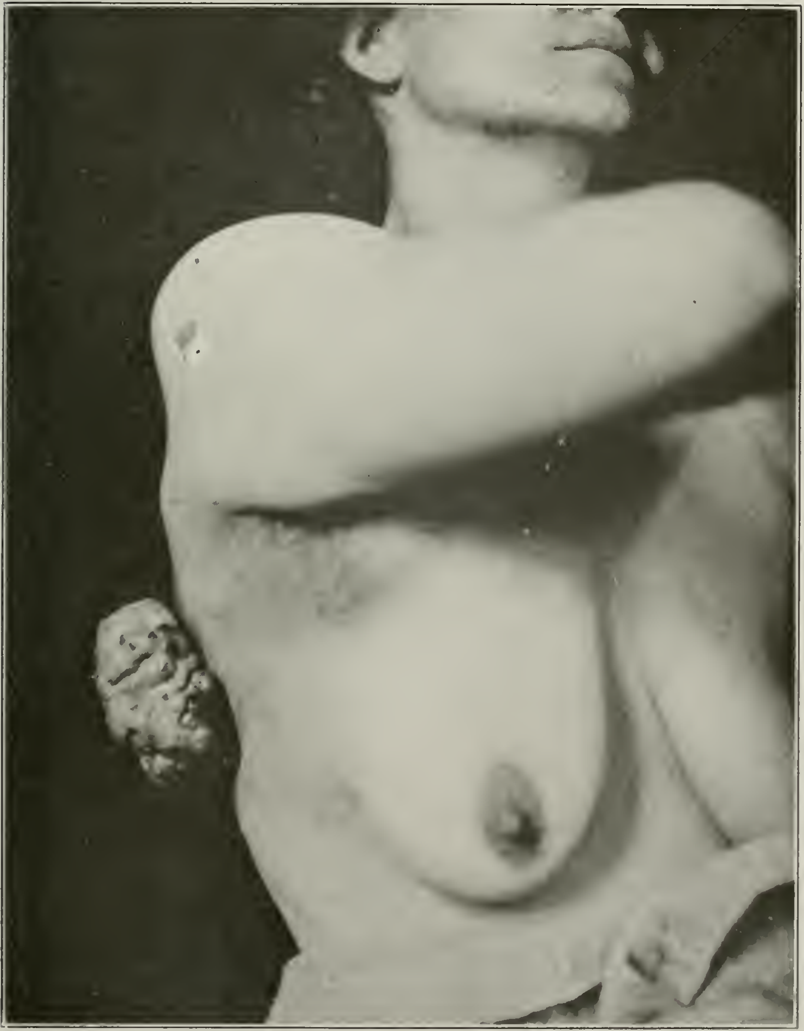


Fig. 1. Case I. Presbyterian Hospital No. 6781. Pedunculated melanocarcinoma at the time of entrance into the hospital.

Past History. Aside from an operation for appendicitis fourteen years ago, she has never been sick. She has had three pregnancies; a stillbirth and two living children who are now in good health.

Family History. Negative.

Physical Examination. In the right lateral costal region is a cauliflower-like tumor (Fig. 1), six inches in diameter, attached to the skin by a small pedicle, around the margins of which in the skin are several nodules of varying size. The surface of the mass is necrotic and discharges a greenish-black foul-smelling exudate. No other moles are found elsewhere in the skin.

In the right axilla and right supra-clavicular regions there are masses of hard glands. There were râles in both lungs.

Diagnosis: "Probably sarcoma of the chest wall."

Course: Dr. Hawkes, the surgeon in charge, decided to remove the primary growth as a palliative measure.

Operation: Oct. 30, 1918. An elliptical incision around the tumor about two inches away from the pedicle was made so as to include the few surrounding nodes in the skin. A plain gauze drain was inserted in the outer end of the wound which was closed with silkworm gut and silk.

After the operation, the axillary glands grew rapidly, causing much discomfort from their size and so a second operation was decided upon.

Pre-operative diagnosis was metastatic sarcoma of axillary glands.

Operation: November 14, 1918. A six-inch incision parallel to the lower edge of the right pectoralis major muscle gave sufficient space for the removal of a dense mass of lymph nodes and adherent connective tissue, the whole thoroughly infiltrated by neoplasm. The operation was of necessity incomplete due to the invasion of chest wall structure by tumor tissue. A gauze drain was inserted in the upper, outer corner of the wound.

X-ray examination on October 29 had shown the presence of nodules in the left lung and so the patient was subjected to twelve x-ray treatments at about five-day intervals, covering the chest anteriorly and posteriorly on both sides. Coley's serum was injected three times, in doses of $\frac{1}{8}$–$\frac{1}{2}$ minims at about four-day intervals.

The wound from the second operation healed rather quickly, but the posterior wound was slow to repair and a number of small tumor nodules developed in the surrounding skin. Throughout her stay in the hospital the woman ran a morning temperature of 100° to 101° until the last two weeks when it occasionally reached 103°. The pulse varied between 80 and 120.

The left axillary nodes, the right side of the tongue, the left inguinal nodes and the right cervical glands then became involved. One hundred milligrams of radium were applied for one hour on two occasions to the tongue with no improvement.

On January 13 the patient had convulsions which left her with facial paralysis and ptosis of both upper lids, and on January 17, after a series of spasmodic twitchings in all her muscles, she died. The immediate cause of death was thought to have been one or more metastases in the brain. Permission for autopsy was not obtained.

First Pathological Report, October 30, 1918:

Gross Examination: The specimen consists of an elliptical piece of skin, 7 × 5 cm., attached by a pedicle 2.5 cm. wide, to a lobulated dense tumor mass, 17 × 15 × 9 cm. (Fig. 2). In spots the surface is ulcerated. On one side the lobulations are small, 0.2 cm. in diameter, but elsewhere they are about 2 cm. in diameter, and their respective stems connect with the main pedicle. The cut section shows an irregular cortex of white tumor tissue conforming to the lobulations on the surface. In the depths of the stroma and actually in the pedicle there are four rounded distinct tumor masses apparently separated from the pedunculated surface lobulations.

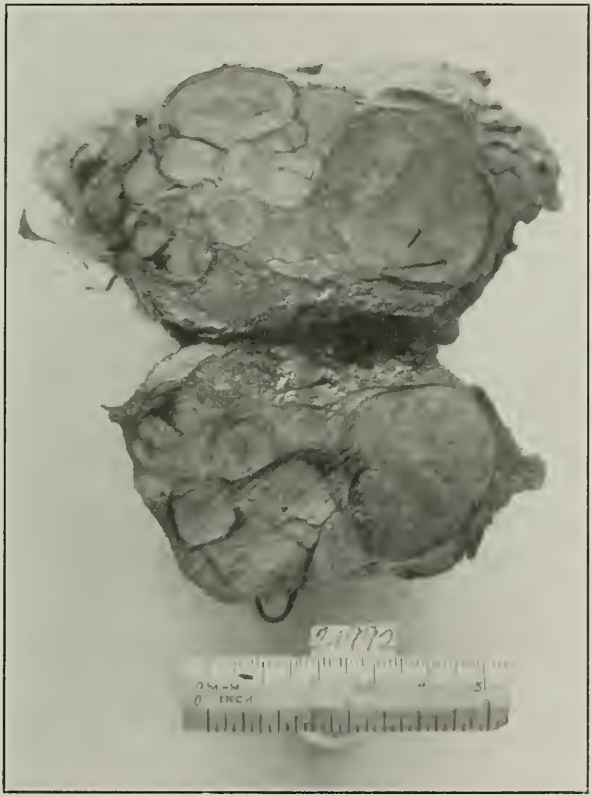


FIG. 2. Case I. Cut section of the tumor.

Microscopic Examination: The tumor mass is divided by very vascular connective tissue into lobules which are further subdivided into alveoli (Fig. 3). These are filled with great numbers of large, sharply outlined irregularly shaped cells of various types. Most of them are round, but there are many others which are fusiform, hexagonal and rectangular in outline. The nuclei are as a rule large and vesicular, but otherwise present all varieties of shapes and positions in a homogeneous pink cytoplasm. Many cells have more than one nucleus—as many as ten being found in one cell. In some cases the cytoplasm of the various cells appears as one homogeneous matrix, whereas in other parts there are definite margins between the cells which have distinctly epithelial characteristics. Vacuoles are common. There are numerous mitoses, and the picture is clearly one of intensive cellular proliferation. There are areas of hemorrhage and round cell infiltration.

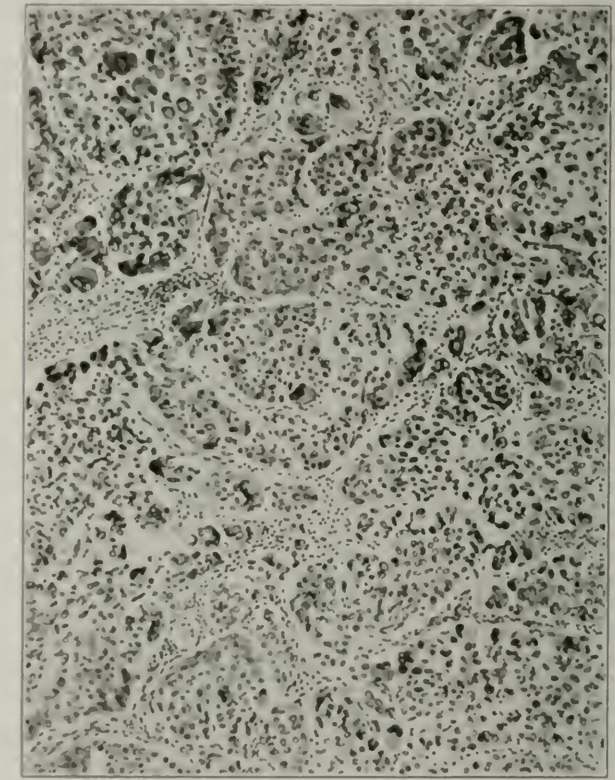


FIG. 3. Case I. Microscopic view of the tumor showing general alveolar configuration.

Diagnosis: Sarcoma of the skin of the lateral costal region.

(N.B. It was not noticed until later that in certain areas there were numerous large non-phagocytic cells filled with brown granular pigment which had the characteristic appearance of melanin.)

Second Pathological Report, November 14, 1918:

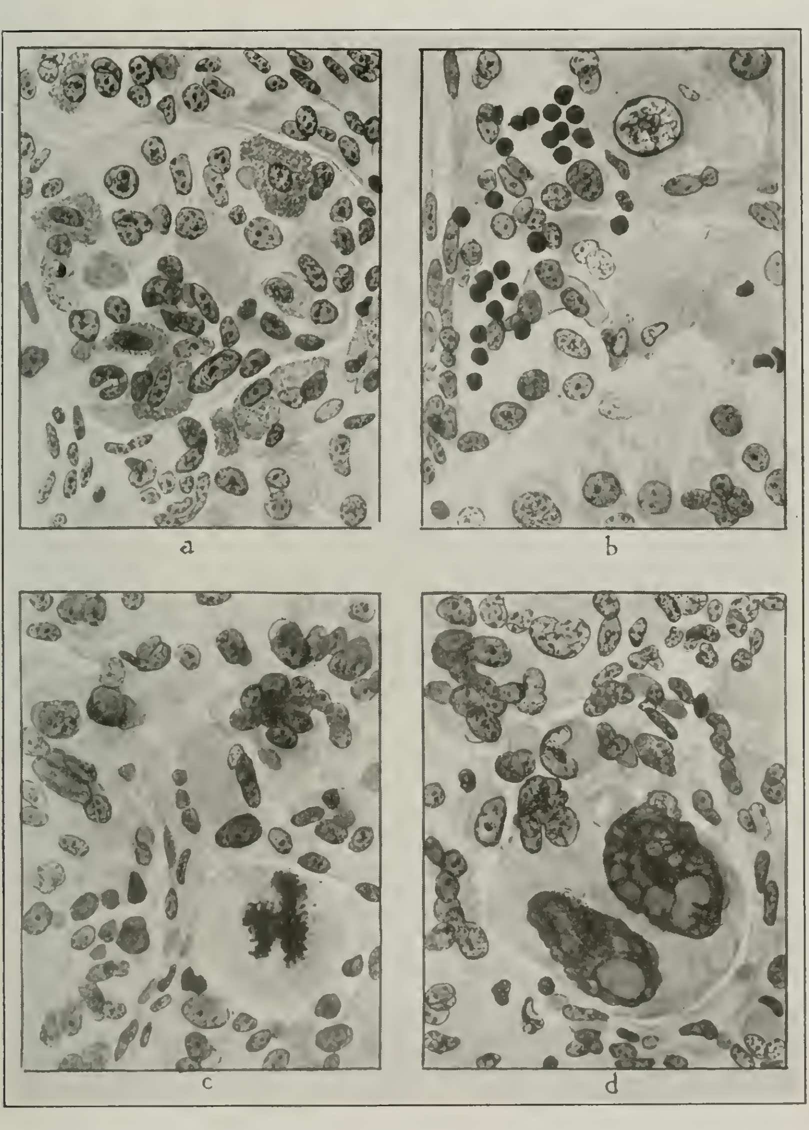


Fig. 4. Case I. High-power view of different areas of the tumor. (*a*) Melanin-containing cells, (*b*) hyalin ground substance, (*c*) mitosis, (*d*) giant cells.

Gross Examination: Specimen consists of a polygonal mass, 10 × 7 × 6 cm. Its outer surface is everywhere roughened where the wound of operation has separated the tumor mass from the surrounding tissue. There are several prominent, irreguarly rounded elevations suggesting an internal lobulation. On cut section, there is found to be an adventitious capsule averaging about 0.75 cm. in thickness, within which there are rounded tumor masses distinct from the fibrous tissue. One of these masses is discolored, apparently from extravasated blood. In general, the tumor tissue is light in color where it is well preserved, but where degeneration has apparently commenced, it has a grayish tinge.

Microscopical Examination: There is an exceedingly loose reticular tissue structure supporting many large sized cells with relatively large, deeply staining nuclei (Fig. 4). Many of these cells have more than one nucleus. All the true tumor cells vary in size, as do also the nuclei within them. In places the tumor cells appear to be formed as if they were syncytial masses. There are scattered areas of hemorrhage and areas of degeneration. There are a few blood vessels of small size with relatively thin walls. A few small areas of lymphoid tissue suggest that the growth has taken the place of a lymph node.

Diagnosis: Metastatic sarcoma of the skin in the axillary lymph glands.

(No pigment-containing cells were found in any of the slides from the axilla.)

After Dr. Mallory had seen the slides and made a diagnosis of melanosarcoma and a number of differential stains had been made to exclude the possibility of the presence of neuroglia fibers, the diagnosis of melanocarcinoma of the skin of the lateral costal region was made by Dr. Clarke.

Case II. No. 15523, D. C., a tug-boat captain, aged 68 years, entered the Vanderbilt Clinic on March 7, 1919, complaining of a growth of the lower mid-dorsal region. Duration—one year.

Present Illness: The patient says that ever since he can remember he had a small, flat, brown mole about 0.5 × 0.75 inches over his lumbar vertebræ. About one year ago it became irritated by his clothing and started to increase in size, until now it is about three inches in diameter. Growth has not been at a steady rate, but has varied, so that at times it has progressed more rapidly than at others. During the last four months there has been an almost continuous watery discharge, often hemorrhagic, which each day soaked through three thick layers of gauze. The tumor is only painful when it is mechanically irritated. The man has had a feeling of heat along the inner side of his right leg during the last few days. He says that he has lost a little weight and strength lately due to anxiety about his condition.

Past History: Negative.

Family History: Negative.

Physical Examination: In the mid-dorsal region, just to the right of the third lumbar vertebra is a lobulated, pedunculated tumor, 7 × 9 cm., elevated about 4 cm. from the skin surface. It is mostly pinkish in color, but is marked with many ulcerating and hemorrhagic areas of various shades of green, red and black. The skin immediately surrounding the growth has a sort of pinkish color. There are many other widely distributed, pigmented moles, some flat and others elevated, in the skin. The main claims that these have existed since childhood.

A rather hurried general examination of the chest and the abdomen was negative. No lymph nodes were found to be enlarged.

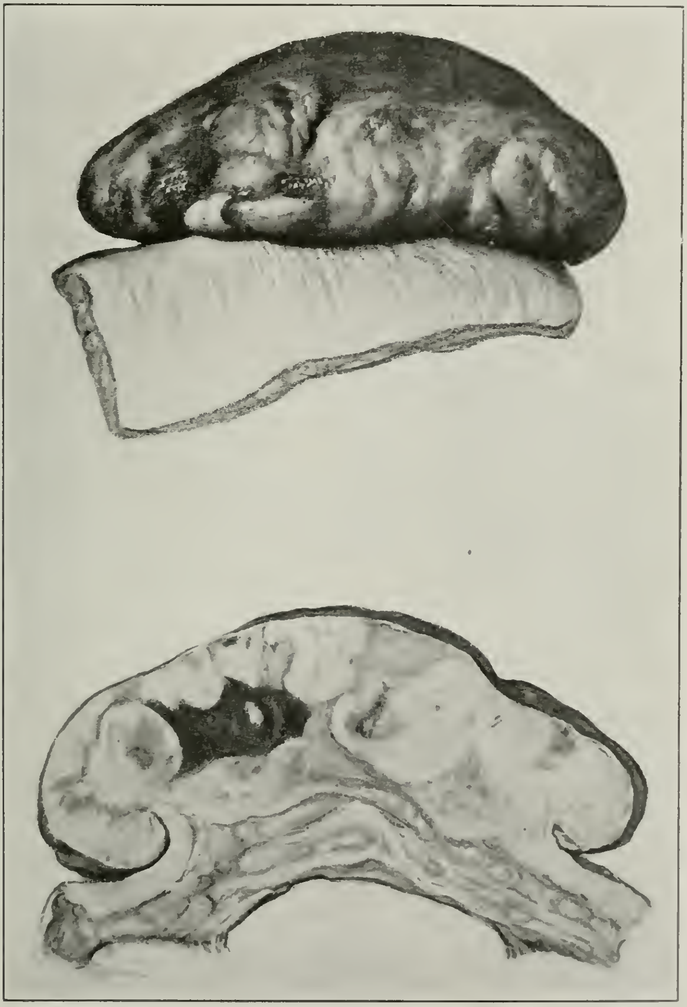


Fig. 5. Case II. Vanderbilt Clinic, No. 15523, Surgical Pathology No. 5410. Cut section of the melano-carcinoma of the skin of the back removed at operation.

Diagnosis: Fibro-epithelial tumor of the skin.

Operation: March 7, 1919. Dr. Loewi removed the tumor by an elliptical incision through the skin, which included some subcutaneous tissue.

Course: The wound is healing as well as can be expected.

X-ray shows an enlarged thoracic aorta and an apparent rarefaction or twisting of the fifth lumbar vertebra, but no suggestive evidence of any metastases.

Pathological Report

Gross Examination: From an irregular area of skin and subcutaneous tissue, 10 × 7 cm., there protrudes a mushroom-like tumor mass, 7 × 7 × 2 cm. (Fig. 5). The pedicle is 4 cm. in diameter. The surface of the growth is rough and lobulated, overhangs the edges, and except for two widely-separated areas, is excoriated and free from epithelium. On cut section, the skin and subcutaneous tissue is about 1 cm. in thickness and is distinct from the tumor proper, which consists of rounded, irregular masses of solid and relatively homogeneous neoplastic tissue. There are some dark areas, apparently due to hemorrhage, one of which is about 0.5 × 1 cm. Gross examination suggests a very cellular type of tumor growth.

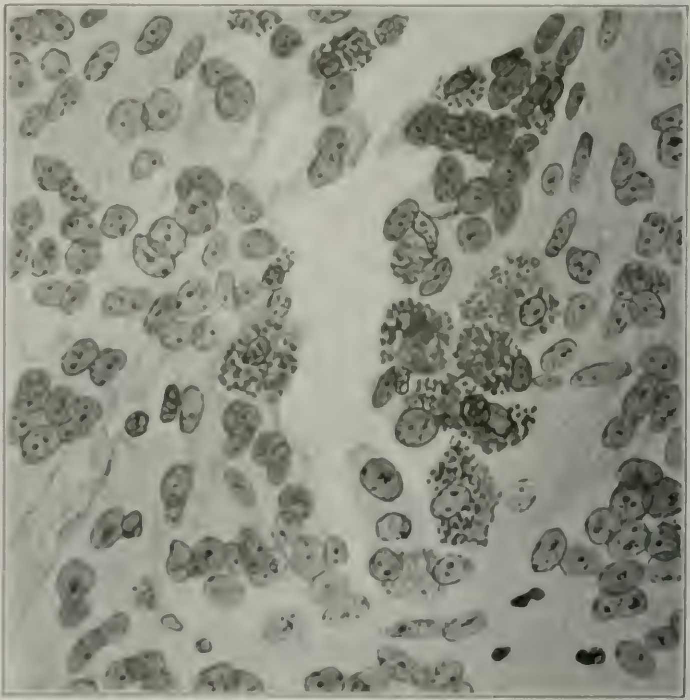


FIG. 6. Case II. Microscopic view of the tumor showing melanin-containing cells.

Microscopic Examination: The section shows that the tumor is composed of a great number of cells closely packed together and divided irregularly by fine connective tissue trabeculæ into alveoli of varying shapes and sizes (Fig. 6). In general the cells have little appreciable cytoplasm, but consist mostly of relatively large oval vesicular nuclei. There are other cells, however, with considerable protoplasm and some with smaller pycnotic nuclei. Numerous pigment-containing cells are found throughout the section; some of these, situated in the trabeculæ, have rather large, light-brown refractile granules which by the potassium ferrocyanide stain are shown to contain iron; whereas others, *i.e.*, the true tumor cells in the alveoli—contain smaller and darker granules which are not differentially stained and have the typical appearance of melanin.

Diagnosis: By Dr. Clarke: Melano-carcinoma of the skin.

In the first case discussed, as the result of a routine morphological examination by the pathologists, who were not aware that the growth originated in a mole, the diagnosis of sarcoma was given. It was not until a second more careful microscopical examination was made that the pigment cells were observed, and in fact these were so few in number that it is perfectly conceivable that sections might have been cut in which there would have been none of them present. There are many such instances in which morphology alone cannot be relied upon in all cases to give the most accurate interpretation of a disease process. In the second case the similarity between it and the previous one was immediately recognized and the diagnosis given on gross examination was made more certain by the knowledge that the growth originated from a mole.

Discussion:

Dr. Moschcowitz: I was rather disappointed that Dr. Murray did not express his views covering the origin of the melano-carcinoma, and the source of the pigment.

Dr. Murray: In regard to the origin of melanotic tumors, the subject has been discussed so many times rather recently by Dr. Coley in this city, Dr. McCarty of the Mayo Clinic, and by others, that I considered these two specimens rather meager material on which to base any new hypothesis. The reasons given by McCarty, who was the last to write on the subject, for believing that the majority of these tumors arose from the epithelium, are subscribed to, I believe, by Dr. Clarke, and for that reason the title of the paper was melano-carcinoma and not melano-sarcoma.

REPORT OF A CASE OF CYST OF THE TESTICLE IN A DOG

ALVAN L. BARACH, M.D.

(From the Department of Surgery, College of Physicians and Surgeons, Columbia University, New York)

The first description of cysts of the testicle is that of Astley Cooper (1) in 1845, under the name of hydatid disease of the testis. He described four cases, and sharply divided them from cysts arising in connection with new growths, which he termed fungoid disease of the testis. There does not seem to be evidence that they were of neoplastic origin, although such an opinion has been recently vouchsafed for them (13). Succeeding accounts were less accurate in differentiating cysts of the testicle from cystic neoplasms. Cases were, however, described by Curling (2), 1850, Hockenburg (3), 1885, and Walliman, (4), 1911. Albert (5) mentions three cysts of the testicle in 6,000 autopsies.

The present case is that of a shepherd dog, nine years old.

Past History. Dog was run over by an automobile when four or five years old.

Present History. Swelling of scrotum was noticed one and one half years ago. Increase in size was gradual. Dog was healthy save for occasional attacks of obstipation lasting three to five days, during which time he gave evidence of being severely prostrated. He had just recovered from such an attack three weeks ago, but was at this time in apparent good health.

Examination. Scrotum was much swollen, spherical, smooth, and fluctuated; it did not transmit light. It could not be reduced into abdomen. One testicle could be made out at the lower extremity of scrotum. No signs of inflammation were present.

Diagnosis. Hernia and hydrocele.

Operation. On incising tunica vaginalis, a smooth rounded cyst was seen. Operation for orchidectomy was done, and cyst and portion of vas removed. At end of operation, a single testicle could be plainly felt in the scrotum. The dog recovered from operation, the wound healed, and he is now in good condition, four months after operation.

Gross Pathology. Surg. Path. No. 5264. Specimen consists of a spherical body, the diameters of which are 7 × 6.5 cm., Fig. 1. In the fresh state, it showed a smooth, glistening surface, fluctuated, and transilluminated light. The surface shows many large injected veins. At a point on one lateral surface there is a bluish, slightly raised area, 3 × 3 cm., which is firm on pressure. On the opposite surface is seen a longitudinal mass, 6 cm. long, 0.6 cm. in width at its central part, and 1.3 cm. at either end. This is clearly the epididymis, and head, tail and body are shown attached to cyst wall. From the tail of the epididymis, the vas is seen to arise and extend upward. Section through the vas shows it to be patent. On opening the cyst, Fig. 2, the surface is seen to be glistening and for the most part smooth. At points there are slight ridges or shelves that project from the wall. From these ridges and also from points on the wall that are relatively smooth, there extend coarse strands that pass to the cyst wall opposite. These form a rough, scanty meshwork in which are deposited small, soft, yellowish masses that vary in size, the largest being about 3 mm. in diameter. There is a thin membrane stretching between some of the strands. Section through the circular bluish mass referred to above shows it to be 8 mm. in thickness at its central part; and from that point it diminishes until it ends in the cyst wall, the thickness of which is 1 mm. At the periphery of the mass, the cut surface is smooth, homogeneous and dark in color. Centrally, it shows several large irregular cystic spaces, is of a lighter color and does not give the compressed appearance of the peripheral portion. The mass is the apparent remains of the testis. It is notable that the intra-

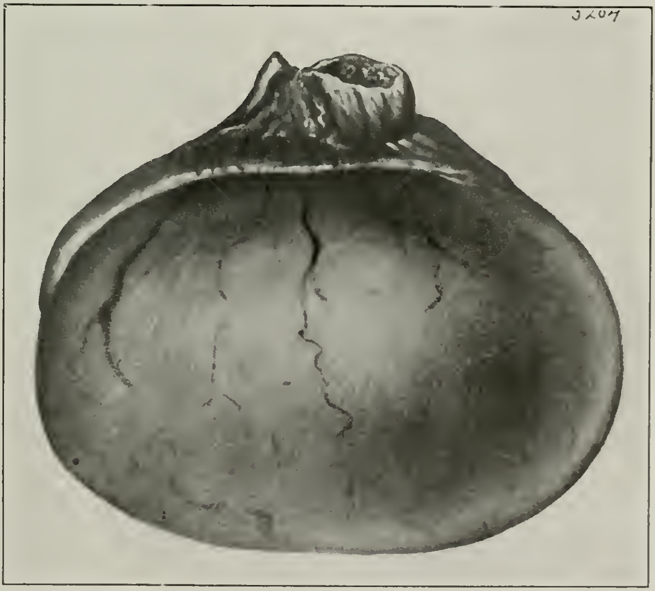


Fig. 1. Surface form of cyst of testicle. Epididymis attached to posterior portion of cyst capsule. Injected veins are seen on the surface. Diameter of cyst, 7 × 6.5 cm.

cystic network is in greater abundance near, and has a more direct connection to, this testicular mass than to any other part of the cyst wall. A few strands reach over to the cyst wall connected to the epididymis. The disposition of these various strands is very suggestive of the fibrous septa that project from the mediastinum to the tunica albuginea. A portion of the peritoneal sac which extended through the inguinal ring is present, attached to the tail of the epididymis and the cyst wall. The sac was closed off, and presented no communication with tunica vaginalis. The serous parietal layer of the tunica vaginalis was continued over the cyst forming the visceral layer of the tunica vaginalis. There was no protoplasmic connection between the epididymis and the testicular mass. The fluid in the cyst was unfortunately not examined.

Microscopic Pathology. Figure 3 represents the circular bluish mass referred to as the remains of the testis. The external covering is of fibrous connective tissue. Considerable hyaline degeneration has taken place throughout the capsule, interrupting the fibers and destroying their parallel arrangement in various places. Beneath the capsule is the parenchyma. This is irregularly divided up by cysts of varying sizes and shapes, many of which are visible with the naked eye. The cysts are lined for the most part by a single layer of elongated flattened cells. Many, however, are lined by cuboidal cells. The majority of the cysts are empty; some contain a homogeneous pink-staining substance, apparently serum; still others contain red blood cells. The cells of the parenchyma are very unusual. They are of two varieties. The more prominent type consists of cords or strands of polygonal epithelial cells with vesicular nuclei. Near the capsule, they tend to be arranged parallel to the surface. More deeply, the arrangement is completely broken up by the cysts. In favorable fields the width of these cords is seen to be made up of two cells. In other fields, the cords do so merge into each other, and are so overlapped by other cells, that such a division is impossible. Where it can be seen, the impression is definitely given of tubules in which the lumina have collapsed, and the lining cells are in opposition. There is a delicate connective tissue framework separating these cords. In places this is apparently absent, the cells resting back to back against each other.

The second type of cell is found in the connective tissue spaces between the cords, and overlapping the cords themselves. It is a rounded, mononuclear cell. The smaller ones have much chromatin and resemble lymphoid cells. The larger ones have abundant cytoplasm, vesicular nuclei, some of them contain brown granules resembling hemosiderin. They have the general form of large mononuclear phagocytes. These cells, especially the small mononuclears, tend to be arranged in groups, although they are seen separately throughout. In this slide, they are numerically few, but in Fig. 4 they are much more common.

Hemosiderin in addition to being contained in the cells can be seen free in the connective tissue spaces. The lining of the cyst is composed of elongated flattened cells. In many places this is destroyed, the epithelial strands projecting into the cyst cavity uncovered.

The tissue is quite vascular, capillaries and larger blood spaces being especially prominent.

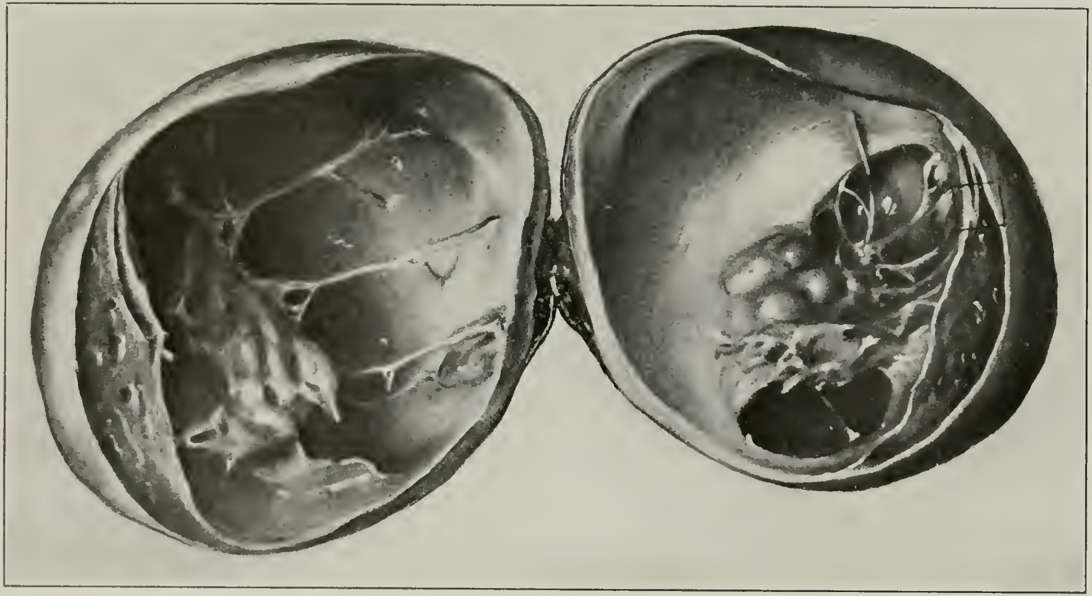


FIG. 2. Interior of cyst. Small cystic spaces are seen in cross-section of remains of testis. Fibrous strands bridge the cavity of the cyst. Thickness of capsule, 1 mm. Thickness of testis, 8 mm. at its widest part.

No functionating or hypertrophied tubules are present. Spermatozoa and the forerunners of the sex cells are nowhere to be seen.

Section (not reproduced). This section was made through a portion of the cyst wall between epididymis and testicle proper. It shows the capsule, and, lining of the inner surface of either extremity, a small mass of testicular tissue resembling that described above. The cords of polygonal epithelial cells here have a more irregular arrangement, giving the impression of being bent on each other. In some places a double layer of cuboidal cells surrounds an epithelial cord, so that it appears as if one cord of cells were being invaginated by another.

The mononuclear cells described above are more frequent here. There are little collections of small round cells and many isolated large mononuclear cells. The latter frequently contain hemosiderin. Here hemosiderin is also present free in the connective tissue spaces.

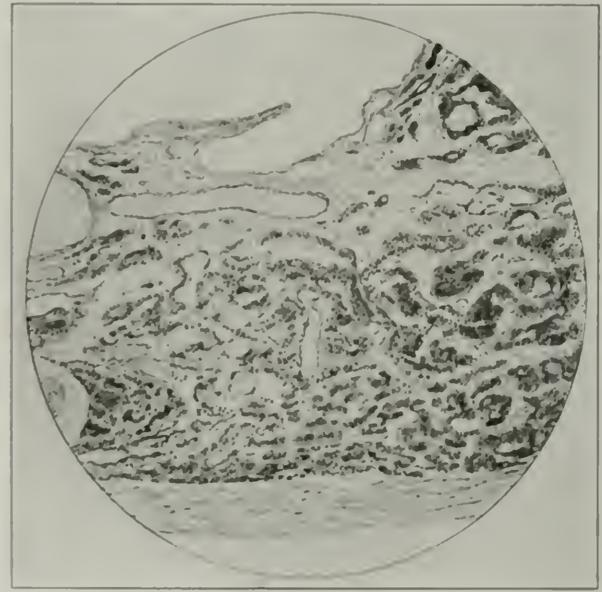


FIG. 3. Low power of testicular mass. Irregular cords of polygonal epithelial cells broken up by cysts. Some of the cysts contain red blood cells. There are many capillaries and wide sinuses in the section. Above is the lining of the cyst, composed of elongated flattened (mesothelial) cells; below is the fibrous capsule.

The blood vessels likewise partake of the irregularity in this section, being more tortuous and more irregularly disposed.

Figure 4. This section was taken through the epididymis, and included

some subjacent testicular tissue. The epididymis reveals no abnormality. The head shows the usual stratified lining epithelium, the surface cells of which are long, narrow, columnar cells, and possessed of cilia. The muscular coats are well preserved. Separated from the epididymis by a dense band of fibrous connective tissue is a small amount of testicular tissue differing completely from that previously seen. Seminiferous tubules are present in varying degrees of function. For the most part they have wide lumina. Frequently these are filled with degenerated and cast off sex cells. Some of the tubules are apparently functionating. They present an outer layer of one to three rows of flattened connective tissue cells. Upon this rests the lining epithelium of spermatogenic cells, first small cuboidal cells with deeply staining nuclei, then several rows of large spherical cells with vesicular nuclei in varying stages of mitoses. Bordering on the lumen are small round cells, a few rod-shaped cells and a very few almost mature spermatozoa. This typical arrangement is only infrequently seen, most of the tubules showing marked disturbance of function. A few have collapsed. Many, however, show dilated lumina and have their epithelium narrowed down to one or two layers of flattened or low cuboidal cells.

In considering the pathogenesis of cysts of the testicle, it is simpler to classify first their modes of origin as either retention cysts or non-retention cysts. Retention cysts may conceivably arise through a blocking of certain portions of the excretory apparatus of the testis, as vas deferens, ducts of the epididymis or seminiferous tubules. Or they arise from some glandular remains, cut off in the process of development, which suddenly receive the stimulus to secrete, as the cysts of the parodidymis. In these cases there is a closed cavity or duct lined by a secreting epithelium. The secretion of this glandular epithelium tends to flatten the lining cells and by gradual distention to compress the adjacent connective tissue so that a capsule composed of epithelium internally, and connective tissue externally, is formed. The cyst contents are derived from the secreting epithelium. Similarly, cysts derived from the blocking of lymphatic channels might be conceived, as hygromata, with the lining here of endothelial origin.

Non-retention cysts may be said to arise in the testicle in connection with one of the following processes: (1) Hemorrhage, (2) necrosis, (3) extravasation of seminal fluid, (4) neoplastic origin. It is the cyst arising as a result of hemorrhage or necrosis that is to be especially considered. (The extravasation of seminal fluid through rupture of tubules can be considered of like nature.)

In the formation of hemorrhagic and necrotic cysts a classical description, that of Adami and Nichols (6), is somewhat as follows: Blood is exuded, and a destruction of inclosed tissue results. Through autolysis and leukocytic agencies, the bodies of the corpuscles, cell débris, and finally the hemoglobin, are absorbed, leaving a clear serous fluid around which a capsule has gradually formed. Descriptions of this character, however, leave much to be desired.

Why is not the hemorrhagic area organized, what causes the formation of an internal lining of flattened epithelial or mesothelial cells, how is the peripheral portion of the capsule, composed of compressed fibrous tissue, to be accounted for, what is the cause of the persistent distention and enlargement of the cyst sac, its swift refilling when emptied? These are some of the questions that lack adequate explanation in the non-retention cysts. William C. Clarke has advanced a hypothesis that meets these questions. He supposes that where cysts are formed as a result of hemorrhage, there are substances present which act in a two-fold manner. (1) They keep the blood fluid, and (2) they raise the osmotic pressure in these cavities. These substances may be of salt nature, varying with each man's individual blood chemistry. This hypothesis explains why connective tissue cells do not organize the hemorrhage, since it has been shown *in vitro* that fibroblasts do not grow into fluid but that they spread themselves about it and form a covering. This has been demonstrated in Dr. Clarke's laboratory by the formation of experimental mesothelium (7). Specially prepared collodion foreign bodies were introduced into the subcutaneous tissue of a dog. Specimens were removed after 20 to 30 days, and the collodion bodies were found covered by elongated flattened cells closely disposed and parallel to the free surfaces. Further experiments *in vitro* showed that cells surrounding serum became elongated and flattened in a similar way. Through the observation incubator it was seen that these cells were derived from connective tissue cells. It was also shown that where open collodion boxes containing serum were placed in the tissues, the serum was not invaded but was always covered by a flattened layer of connective tissue cells. Thus it was demonstrated that connective tissue surrounding a relatively non-irritating foreign body as collodion or serum, would form a lining pavement mesothelium composed of elongated flattened cells. In these cases, no capsule was formed, no fluid distending the cavity occurred, and a cyst could not be said to have been produced. It was stated above that the substances that kept the blood fluid also raised the osmotic pressure within the cavity. With higher osmotic pressures obtaining, the fluid elements of the blood and lymph diffuse into the space and cause increasing distention. The bordering connective tissue cells become flattened to form a mesothelial lining, as explained above, and, in addition, the distending pressure is transmitted peripherally, causing compression of the adjacent connective tissue and ultimately its fibrous capsule. The increasing contents of the gland and the formation of the capsule can thus be explained in these non-retention cysts. In retention cysts, the secretion of the lining cells is held to be the factor that distends the cavity and causes mechanical flattening pressure on the lining cells. It is this same secretion that causes the cyst to fill up again when its contents have been evacuated. In non-secretory cysts this mechanism is absent, and the hypothesis of Clarke is adequate to explain these above-named phenomena. Mere fluidification of hemorrhagic and necrotic contents would presumably not cause progressive flattening pressure, progressive distension, and reaccumulation of fluid. The supposition might be offered that the connective tissue cells in the presence of fluid take on by metaplasia a secretory activity, but this finds no convincing analogy in cellular pathology elsewhere.

An interesting corollary to the hypothesis of Clarke is found in recent work on fibrinolysis. In brief, it was observed by Goodpasture (8), that a clot formed from the blood of people who had cirrhosis of the liver autolyzed in 3 to 12 hours, leaving clear serum. If blood is drawn from a relatively normal individual into a sterile flask, it will remain clotted a week or longer, thereafter slowly dissolving. In certain people, especially in those suffering from cirrhosis, and in dogs injected with proteoses or poisoned by phosphorus, a clot forms, but the fibrin autolyzes, leaving, in three to four hours, the fluid serum. So that in these conditions, hemorrhage occurring in the tissues, instead of clotting, forming a fibrin meshwork and then organizing, undergoes fluidification. In fact, in one of the cases reported by him, autopsy immediately after death showed a fluid pond the size of an egg in the subcutaneous tissue of the abdominal wall. No evidence of clot was present. What would have happened to this collection of serum in a confined space is difficult to tell. In the light of the experiments in the observation incubator above mentioned, it does not seem too much to say that a lining membrane of flattened mesothelial cells would have formed about it. Thus we would have an abnormal collection of fluid, surrounded and localized by a pavement lining derived from connective tissue. Whether this pond of blood would have in addition acquired a fibrous capsule and show a tendency to increase in size can be matters for speculation only.

However, the mechanism of fibrinolysis, or fibrin solution, also possesses interest in line with the hypothesis which has been discussed. It is known that fibrin dissolves in dilute solutions of certain salts as NH_4, SO_4, KNO_3, Na_2, SO_4, NaCl (9). That the lysis of fibrin in the tissues is dependent on the action or presence of salts has not been shown. Conceivably, however, the dissolution of fibrin may be due to salts acting alone, to enzyme action plus the presence of salts acting as a catalyzer, or to enzymes alone. It has been reasonably proved that whatever is the acting substance, it is contained in the leukocyte (10). The aggregation of leukocytes is needed for the solution of the fibrin. The opinion of Dastre (10, 11), who first called attention to fibrinolysis, is that salts are the important substances. If this latter statement is verified, it may be said that salts present in sufficient quantity to cause solution of the fibrin, may raise the osmotic pressure of the cavity in which they are contained. Conditions are then favorable for a diffusion of liquid into a region of higher osmotic tension. In this way increasing distention and pressure by the fluid would accomplish the remainder of cyst production. The supposition of the presence of salts is considered because of its suggestive value. That salts are present in increased quantity in these cavities has not been shown nor, as far as I know, attempted. It is thought by Goodpasture that enzymatic action is the basis of fibrinolysis.

There is then the theory that salts may be present in hemorrhagic cavities acting both as catalyzers to fibrinolytic enzymes and as osmotic tensors. The quantitative and qualitative variations in these salts would depend on the individual, so that a determining factor in the development of cysts following extravasation of blood would lie in the tissue and blood chemistry of the individual, just as now it is known that certain clinical conditions which have a definite chemical basis, determine whether blood will clot and organize, or liquefy.

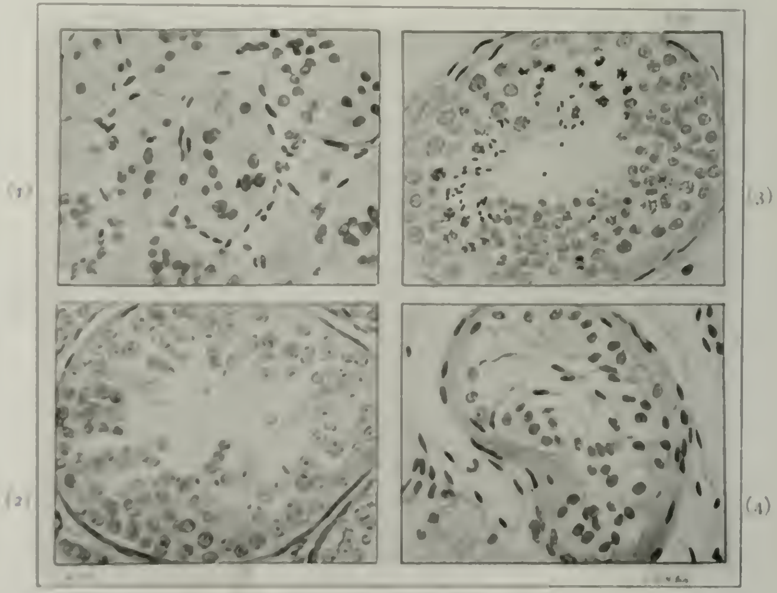
A few cysts of the testicle following trauma and hemorrhage have been described, but in all except one neoplasm developed. In this one the description is hardly adequate (14).

Hemorrhagic and degeneration cysts are said to occur in the brain following anemic infarction, in old gummata or abscesses in the tissues, in corpora lutea, in the bone marrow of old age, in the thyroid, pancreas, kidneys, and spleen (12).

Cysts arising in connection with neoplasms may find their origin in hemorrhage or necrosis, or in the secretion of abnormally enclosed glandular epithelium. Cystic neoplasms of the testis have been recently claimed to be of teratomatous nature (13), in which case their origin is probably from the embryonal development of the sexual blastomeric cell, as other structures of teratoma are developed. Here, too, however, the development of blood cysts is possible, for, in fact, the majority of the cysts described by Ewing in his series of teratomata showed the presence of bloody fluid (13).

The cyst here reported is considered a non-neoplastic, non-retention cyst of the testis having its origin in hemorrhage or degeneration, with trauma as a possible etiological factor.

There is no evidence that this is a neoplasm. The essential cells, though unusual, show a certain uniformity in size, shape, and arrangement, which is not expected in a tumor. This arrangement, as was described, is frequently broken up by cysts, but evidence of its basic similarity is to be found in the different sections. Mitotic figures, apart from the area of spermatogenic cells, are nowhere seen. Further, the essential cells do not arise in the rete testis, as tumors of the testis have been shown to do since Curling (2) first pointed it out. These cords of epithelial cells rather present the picture of atrophic tubules with collapsed lumina. Comparison with a cryptorchid testicle of a man, 22 years old, demonstrates a certain similarity. The cells, though



Section 4. High power. (1) Testicular mass. Polygonal cells arranged in cords two cells wide giving the appearance of atrophic tubules with collapsed lumina. Smaller groups of mononuclear cells present in connective tissue framework. (2) Relatively normal tubule of a dog's testicle. (3) Relatively normal tubule from a human testicle. (4) Tubules of a cryptorchid adult human testicle, showing tendency toward obliteration of lumen.

differing from those in the present case, tend to be opposed to one another, in some places completely obscuring the lumen. The testicle of a seven-months' human fetus shows also a lack of lumen in the seminiferous tubules. In all these cases, including the one under consideration, the lack of active function may account for the absence of lumina, and the consequent apposition of adjacent cells.

The cyst does not give evidence of being a retention cyst. The vas is patent, the epididymis is not affected. Further proof of its being a cyst of the testis proper is the arrangement of the fibrous strands in the cyst cavity quite apart from the epididymis, and also the disposition of the atrophied tubules lining the inner surface of the capsule. The epididymis is healthy and undisturbed. Blocking of the seminiferous tubules does not seem to have taken place. Except for the small area of partially functionating seminiferous tubules, there are no patent tubules, no wide dilatations and enlargements, and no evidence of spermatozoa. The persistence of some testicular tissue beneath the epididymis may be ascribed to the protecting influence that the margins of the epididymis had. That this is not of tubular origin, and, as such, a spermatocele, cannot be rigorously denied, but it seems unlikely. The fact that cysts occur only in the area of atrophic cells, or the epithelial cords, and none in the partially functionating tissue, is strong evidence that the cysts did not originate there. Had that been so, some of the smaller cysts would probably have been found alongside dilated tubules.

The multiplicity of the cysts suggests a degeneration phenomenon as in the cystic degenerations of the ovary. This could of course occur just as easily with numerous areas of hemorrhage. Further, the presence of hemosiderin free in the connective tissue spaces, and inclosed in the large mononuclear cells suggests that it is of hemorrhagic origin. The history of severe trauma can be added. So that by exclusion and *prima facie* evidence, this cyst can be considered probably of hemorrhagic origin, or of hemorrhagic and degenerative origin. The old age of the dog suggests that degeneration played a part.

CONCLUSIONS

1. The explanation of the mechanism of a retention cyst is adequate within the limits of our present knowledge. The damming back of secretions in an epithelial lined cavity closed off in post-natal life or congenitally accounts for the accumulation of cyst contents and the formation of a cyst capsule.

2. The pathogenesis of non-retention cysts has not been adequately explained. The supposition has been made by William C. Clarke that there are in hemorrhagic and necrotic cavities substances which raise the osmotic pressure and induce filling of the cavity and capsule formation. These substances may be of salt nature and perform the two-fold mechanism of keeping a fluid medium and acting as osmotic tensors.

3. The phenomenon of fibrinolysis affords an interesting corollary to this hypothesis. Through its agency hemorrhage may take the form of an unclotted fluid pond. Further, the mechanism of fibrinolysis may prove to be dependent in part on salts present in the tissues.

4. The case reported is considered a non-neoplastic, non-retention cyst of the testis. Its pathogenesis is considered as arising from hemorrhage or degeneration, or from both. Trauma is a possible etiological factor.

Bibliography

1. Cooper, A. P.: Observations on Structure and Diseases of the Testis London, 1841, 2d ed.
2. Curling, T. B.: Observations on cystic diseases of testicle. *Med. Chir Tr.*, London, 1853, xxxvi. Treatise on diseases of testes, 1866.
3. Hockenburg, I : Neber cysten am Hoden und Hebenhoden. *Med. Jahresb.*, Wein, 1885, xv, 149.
4 Walliman, G.: Contribution a l'étude des kystes spermatiques. Paris thesis, 1911.
5 Albert: Traité de Chir. clin. et de Med. Op., Paris, 1893, 1, iv.
6. Adami and Nichols: General Pathology, volume 1.
7. Clarke, William C.: Experimental Mesothelium. *Anat. Rec.*, 1916, x, 301.
8 Goodpasture, E. W.: Fibrinolysis in chronic hepatic insufficiency. *Bull. Johns Hopkins Hosp.*, 1914, xxv, 33.
9. Nolf, P., *Arch. internat. de physiol.*, 1904, 1, 132.
10 Rulot, H., *Arch. internat. de physiol.*, 1904, 1, 152.

11. Dastre, A.: *Arch. de physiol.*, 1893, v, 661.
12. Warthin, A. S.: Reference Handbook of the Medical Sciences, 2d ed., 1901, iii, 348.
13. Ewing, J.: Teratoma testis and its derivatives. *Surg., Gynec., and Obst.*, 1911, xii, 230.
14. Packard: Cystic disease of the testicle from injury. *Am. Jour. Med. Sc.*, 1867, N. S., 135.

A CASE OF CHRONIC CECITIS OF UNKNOWN ORIGIN

A. O. WILENSKY, M.D.

(From the Pathological Laboratory, Mount Sinai Hospital, New York)

The specimen which I have to present was removed from a young man in his early twenties. The patient has never been very robust; and I think that this deficiency is mostly due to the fact that for many years he has suffered from a recurrent and intractable colitis. The dominant features of his intestinal condition are a variable amount of abdominal cramps, a profuse diarrhea, and more or less prostration; the stools have never contained blood or other pathological elements. Dr. Eli Moschcowitz, who has had the man under his care, has never been able to find any adequate etiology for this colitis.

In May, 1918, the patient developed an acute appendicitis, and I was privileged to operate upon him at that time. He had a gangrenous, perforated appendix with a small-sized abscess, and, as far as I could determine, there was no extraordinary thickening of the wall of the gut walling off the abscess beyond what one commonly sees in these conditions. The appendix was removed, the abscess was drained, and an uneventful convalescence and healing of the wound followed. The boy went home apparently perfectly well. The attacks of colitis, however, continued to occur as heretofore.

Two or three months later the patient began to complain of cramp-like pain in the locality of his operation. Dr. Moschcowitz thought he could palpate a mass; I was under the impression that the mass was a distended coil of gut. As the months went on the condition became worse, and the mass became more and more distinct, painful and tender. From time to time the colitis recurred. Finally in February of this year I operated upon the patient again. At the operation there were a moderate number of adhesions surrounding the site of the old operation, but these were no more than one would expect to find. A short section of the cecum and ascending colon was remarkably thickened, and it was rather difficult to make out with what one was dealing; it was interpreted as either a tuberculosis or a lymphosarcoma. The affected portion (the ileo-colic junction) was removed.

The specimen consists of six inches of the ascending colon, the cecum, and two inches of the terminal ileum; the site of the old appendix stump is not made out at all. For a distance of three inches upwards from the caput the bowel is much thickened and rigid; however, no stenosis of the lumen has occurred. Just above and below this process the bowel wall is normal. In the affected portion the mucosa is rather thin, but there are no ulcerations or other abnormalities to be seen. The thickening involves all the layers of the bowel wall; these have been so fused together that the various layers are indistinguishable. No glands are present in the portion of the mesentery removed.

Microscopically the process is of an inflammatory nature and has involved the entire thickness of the bowel wall in rather a uniform fashion. The chief characteristics are large collections of small round cells in which there are thickly dispersed numerous tubercle-like structures. These are small collections of necrotic and partially disorganized cells surrounded by layers of small round cells in which are found giant cells, which, however, resemble in no way typical Langhans cells. The diagnosis has been much in doubt; either there was an atypical form of tuberculosis, or there was a syphilitic element present in the lesion; it could also very well be some extraordinary inflammatory lesion, with the etiology of which we are unacquainted. The Wassermann test is negative and we have been unable to demonstrate spirochetes; the complement fixation test for tuberculosis is also negative and we have been unable to demonstrate tubercle bacilli in the sections. Altogether it has seemed to us that the lesion is unusual, if not new; and beyond the broad conception that the picture is that of a distinctly inflammatory nature, we have been unable to go in our interpretation of the demonstrated pathology.

Within the last week or ten days, the patient has had another attack similar to those which occurred prior to his second operation. The seat of this was directly above the line of division of the ascending colon. Possibly a new and similar lesion is developing at that point.

Discussion:

Dr. Ewing: The gross anatomy of this lesion recalls the lymphogranulomas of the large intestine, and the microscopic structure is not sufficiently distant from what one sometimes sees in typical lymphogranuloma as to render the suggestion of the gross anatomy unlikely. One not infrequently sees lesions which resemble tubercle but which do not respond to the ordinary tests for tubercle. It is these lesions which to my mind have always suggested a relation between lymphogranuloma, lymphosarcoma, and tuberculosis. I think somewhere in that field this lesion is bound to lie. If one regards all three of these diseases as distinct, then to class the present case in this group does not mean very much, but to one who thinks lymphogranuloma, lymphosarcoma, and tuberculosis are closely associated, the assignment to that category is significant. I think one not infrequently sees just such lesions as this which are not quite typical Hodgkin's disease, and still are not ordinary large celled lymphosarcoma. I believe these are all various manifestations of the same type of infection. In a case of this sort one ought to inoculate. Pathologists and surgeons ought to be ready to take such material at the operation and put it into several guinea-pigs.

Dr. Eggstein: I would like to refer to a case that was autopsied at the Presbyterian Hospital. It was that of a man about twenty-seven years old who had a very acute attack of illness simulating acute appendicitis. At operation the surgeons failed to find the appendix very much changed, but they found a hard mass involving the ascending colon, and extending laterally. The lumen of the colon was constricted as a result of this pathology, and a lateral anastomosis of the ileum to the colon was done. The anastomosis failed to unite and the patient developed a general peritonitis and died. At autopsy there was a large ulcerated area at the end of the ileum and here the gut wall was thickened and hard. The cecum and the wall of the ascending colon were ulcerated and showed thickened, indurated walls. The lumen of the gut in the ascending colon was greatly constricted. The thickened intestinal walls were intensely infiltrated with lymphocytes; no distinct giant cells were noted. The lymphocytes were closely infiltrated around the blood vessels and numerous plasma cells were mixed among the lymphocytes. There was considerable increase in the connective tissue. Following the operation a Wassermann test had been ordered and the patient's serum showed a ++++ reaction. The areas in the intestines were diagnosed anatomically as syphilitic. The similarity of this case to the one here reported is most striking.

Dr. Ewing: I think that the result of the surgical operation may determine something in regard to the nature of this case. If it is a lymphosarcoma it will recur promptly and the operation will prove useless.

Dr. Moschcowitz: I have seen this boy for three years, and he gave the history of having had diarrhea for some years previous to that. At present he is feeling well and gaining weight. I think under such circumstances a diagnosis of Hodgkin's disease or lymphosarcoma is hardly probable.

Dr. Wilensky: I think the picture and the clinical progress of the whole disease is almost sufficient to rule out any possibility of lymphosarcoma. I think the lesion must be some kind of an inflammatory condition which has something intimately to do with the colitis. There is one other possibility, and that is, in between the primary colitis and the second operation there was the appendix operation, and it is barely possible that some sort of foreign body was left in, which had given rise to the induration of the wall of the colon. I hardly think this supposition to be likely, but still one should think of it.

SUGAR TOLERANCE IN CANCER

G. L. ROHDENBURG, M.D., ADOLPH BERNHARD, B.S., AND
OTTO KREHBIEL, M.D.

(From the Pathological Laboratory of the Lenox Hill Hospital in the City of New York)

This paper was published in the *Journal of the American Medical Association*, 1919, 72, 1528.

Discussion

Dr. Wood: This is interesting from a diagnostic point of view, but it seems to me that at the present time it is quite useless to speculate about the growth of carcinoma and the sugar curve. It hardly seems probable that the small amount of epithelium growing in the body has the capacity to influence the general metabolism. The curious thing about the matter is, as Dr. Rohdenburg did not mention, that this curve may exist after the carcinoma has been removed. The point of the matter is that it may be a general systemic condition in carcinoma patients, but farther than that one should not go. The position is similar to that after the Wassermann reaction was devised; first it was specific and then it was not specific. Now all that can be done is to make a large series of observations on patients with carcinoma and on others without it, and to see if it exists in children, so that there is a great deal of work to be done. Still, Dr. Rohdenburg has done enough to show that it is certainly, as far as we can judge at present, of value in diagnosis.

Dr. Ewing: I think the point of this sugar tolerance question is that we ought to deal with carcinoma of the stomach, or carcinoma of the uterus, or carcinoma of the breast, but not with all three of them grouped together, because in many respects they are quite different. I should not assume that carcinoma of the testis would have the same relation to metabolism as a general carcinoma of the stomach.

Dr. Moschcowitz: I would suggest if you continue this work that instead of using the alimentary method of testing sugar tolerance you do it with the Janney method.

Dr. Rohdenburg: I might remark that we have a series in which epinephrin was used instead of glucose, and the same curves were obtained. The paper was presented not with any claim of introducing this as a diagnostic method, but simply as an interesting observation. I should hate to have the members of the Society think that the observation has been advanced as anything more than one which has possibilities. As far as the theoretical explanations are concerned, one I think is as good as another. Dr. Ewing's suggestion for the present cannot be carried out, because of small numbers of cases. I shall bear it in mind in our final report.

THE PRODUCTION OF NONSPECIFIC BACTERICIDAL SUBSTANCES BY MEANS OF STAPHYLOCOCCUS AND STREPTOCOCCUS VACCINES IN VIVO AND IN VITRO

A Repetition of Some Work of Sir Almroth Wright

R. OTTENBERG AND K. WALLACH

(*From Mount Sinai Hospital, New York*)

In the *Bulletin of The Académé des Sciences* for October 21, 1918, page 600, Sir Almroth Wright presented a paper on "The Production of Nonspecific Bactericidal Substances by Means of Staphylococcus and Streptococcus Vaccines in Vivo and in Vitro." In his article it was claimed that the mixture of staphylococcus or streptococcus vaccines with blood either *in vivo* or *in vitro* resulted in the elaboration, in all likelihood from the leucocytes, of nonspecific bactericidal substances which acted on either one of these organisms. If this were true it would be of great importance and would probably be of immediate value in practical therapeutics.

We are asked by the Division of Medicine and Related Sciences of the Council of National Defense to repeat Wright's work. We carried out his *in vitro* experiments both with staphylococcus and streptococcus. The method consists of mixing one portion of a dilute vaccine suspension with nine portions of freshly drawn blood, allowing the mixture to clot, incubating at 37° Centigrade for three hours, separating the serum, and then testing the bactericidal power of the serum so treated by mixing a uniform amount of it with progressive dilutions of twenty-four-hour broth cultures of staphylococcus and of streptococcus.

As controls, the same individual serum (which instead of being mixed with 1 in 10 vaccine was mixed with 1 in 10 saline solution), and also the same dilutions of culture, with no serum at all, were set up mixed with equal amounts of bouillon. In each instance several different dilutions of the vaccine were used. The blood was obtained from a normal individual in each experiment.

The vaccines were made by the growth of staphylococcus aureus for twenty-four hours in plain bouillon 1 per cent. acid in flasks. The organisms were then centrifuged so as to get rid of culture medium. They were washed once in 0.9 per cent. sodium chloride solution, then resuspended in saline solution, killed by heating at 56° Centigrade for one hour and counted and diluted according to Wright's method. The preparation of the streptococcus vaccine was the same except that glucose serum bouillon was used because the hemolytic streptococcus employed did not grow very satisfactorily on plain bouillon. In the latter half of the work neutral bouillon was used instead of bouillon 1 per cent. acid, as it was thought that possibly the slight acidity of the bouillon might have impaired the power of the bacteria to stimulate the production of non-specific bactericidal substances.

The bactericidal tests were made in small test tubes and the amounts, 0.2 c.c. of serum and 0.2 c.c. of diluted twenty-four-hour bouillon culture of the respective organism, were measured out with graduated pipettes, a fresh sterile pipette being used for each measurement so that by no chance could bacteria be carried from one tube to another. The mixtures of serum and culture were allowed to stand over night in the thermostat, then 1.0 c.c. of bouillon was added to each tube and after another twenty-four hours in the thermostat, the results were read by microscopic examination of a hanging drop from each tube.

The experiments both with staphylococcus and streptococcus cultures were repeated four times using staphylococcus vaccine three times and streptococcus vaccine once. The appended protocols show the results were entirely negative. In fact on several of the occasions the results were diametrically opposed to those of Wright in that the normal bactericidal property of the serum was impaired instead of increased by the mixture of vaccine. On account of these findings we did not proceed to repeat the *in vivo* experiments.

Unfortunately there are several points, notably in the method of preparing the vaccines, on which Wright gives no details. It is possible for example that some peculiarity in the mode of preparation of the vaccine may be essential.

Therefore, we do not wish to be understood as saying that Wright's work is wrong, but merely that by repeating it as accurately as his published description permits, we were unable to obtain the same results.

EXPERIMENT OF DECEMBER 11

Staphylococcus aureus vaccine
  a. 1,000 per c.c.
  b. 25,000 per c.c.
  c. Saline solution 0.9 per cent.
} 1.5 c.c. of each mixed with 13.5 c.c. of blood.

The mixtures were incubated four hours in the thermostat and the serum separated. Then 0.2 c.c. of each serum was measured into each of 12 tubes. To the tubes were then added in the separate experiments 0.2 c.c. of:

A. Staphylococcus aureus twenty-four-hour culture in plain bouillon diluted $^{1}/_{1000}$ in the first tube, and in each succeeding tube diluted with a double volume of bouillon.

B. Streptococcus hemolyticus twenty-four-hour glucose broth culture diluted $^{1}/_{500}$ in the first tube, and then diluted with a double amount of bouillon again in each succeeding tube.

After twelve hours in the thermostat 1.0 c.c. of bouillon was added to each tube.

+ equals growth of staphylococcus or streptococcus;
— equals absence of any growth.

A. Actual Dilutions of the Cultures	1 1,000	2 3,000	3 9,000	4 27,000	5 81,000	6 243,000	7 729,000	8 2,187,000	9 6,561,000	10 19,683,000	11 59,049,000	12 177,147,000
Staphylococcus culture 0.2 c.c.												
Bouillon 0.2 c.c.	+	+	+	+	+	+	+	+	+	+	+	+
Serum from blood which had been mixed with saline 0.2 c.c.	+	+	+	+	+	+	+	+	+	+	+	—
Serum from blood which had been mixed with vaccine 0.2 c.c. 1,000 staphylococci per c.c.	+	+	+	+	+	+	+	+	+	+	+	+
Serum from blood which had been mixed with vaccine 0.2 c.c. 25,000 staphylococci per c.c.	+	+	+	+	+	+	—	+	+	+	+	—

B. Actual Dilutions of the Cultures	1 500	2 1,500	3 4,500	4 13,500	5 40,500	6 121,500	7 364,500	8 1,093,500	9 3,280,500	10 9,841,500	11 29,524,500	12 88,573,500
Streptococcus culture 0.2 c.c.												
Bouillon 0.2 c.c.	—	—	—	—	—	—	—	—	—	—	—	—
Serum from blood which had been mixed with saline 0.2 c.c.	+	+	+	+	+	+	+	—	—	—	—	—
Serum from blood which had been mixed with vaccine 0.2 c.c. 1,000 streptococci per c.c.	+	+	+	+	+	+	+	+	+	+	+	—
Serum from blood which had been mixed with vaccine 0.2 c.c. 25,000 streptococci per c.c.	+	+	+	+	+	+	+	+	+	+	—	—

EXPERIMENT OF JANUARY 8

The same technic as previously described was carried out, but the vaccine was of a hemolytic streptococcus and the dilutions used were:

25,000 cocci per c.c.
1,000 cocci per c.c.
100 cocci per c.c.

The cultures in the bactericidal experiments were twenty-four-hour broth cultures on neutral bouillon, but the initial dilutions were

Streptococcus culture 1–5,000.
Staphylococcus culture 1–100,000.

Each successive dilution was made by taking 1.0 c.c. of the preceding dilution plus 2.0 c.c. of bouillon.

A. Actual Dilutions of the Cultures	1 100,000	2 300,000	3 900,000	4 2,700,000	5 8,100,000	6 24 300,000	7 72,900,000	8 218,700,000	9 656,100,000	10 1,968,300,000	11 5.404,900,000	12 17.714.470,000
Staphylococcus culture 0.2 c.c....... Bouillon 0.2 c.c....................	+	+	+	+	+	+	+	+	—	—	—	—
Serum from blood which had been mixed with saline 0.2 c.c.	+	+	+	+	+	+	+	—	—	—	—	—
Serum from blood which had been mixed with vaccine 0.2 c.c., 100 staphylococci per c.c.............	+	+	+	+	+	+	+	—	—	—	—	—
Serum from blood which had been mixed with vaccine 0.2 c.c., 1,000 staphylococci per c.c.............	+	+	+	+	+	+	+	+	—	—	—	—
Serum from blood which had been mixed with vaccine 0.2 c.c., 25,000 staphylococci per c.c.............	+	+	+	+	+	+	+	+	—	—	—	—

B. Actual Dilutions of the Cultures	1 5,000	2 15,000	3 45,000	4 135,000	5 405,000	6 1,215,000	7 3,645,000	8 10,935,000	9 32,805,000	10 98,415,000	11 295,245,000	12 885,735,000
Streptococcus culture 0.2 c.c. .... Bouillon 0.2 c.c....................	—	—	—	—	—	—	—	—	—	—	—	—
Serum from blood which had been mixed with saline 0.2 c.c.	+	+	+	+	+	+	+	+	+	+	+	+
Serum from blood which had been mixed with vaccine 0.2 c.c., 100 streptococci per c.c.	+	+	+	+	+	—	—	+	—	+	+	—
Serum from blood which had been mixed with vaccine 0.2 c.c., 1,000 streptococci per c.c.	+	+	+	+	+	—	—	+	—	+	+	—
Serum from blood which had been mixed with vaccine 0.2 c.c., 25,000 streptococci per c.c.	+	+	+	+	+	—	—	+	—	+	+	—

Discussion

Dr. Ewing: May I ask what was Wright's idea?

Dr. Ottenberg: Wright proposed to put this to therapeutic use. If you can increase the bactericidal power of a normal individual's blood you can then inject it into an infected person and increase the bactericidal power in his blood. Wright has not gone so far as to do this, but he proposes to treat the blood of a healthy individual with vaccine and then one or two hours later to do a transfusion into a person with an infection such as bacteremia, for instance. Undoubtedly if the principle works it will be put to that use, and so it is very important to see if it works.

Dr. Ewing: I would like to say that the idea is not new, although the technique may be. Many years ago Elser submitted a man to treatment with streptococcus inoculations, and his blood was used to treat a case of malignant endocarditis.

CARCINOMA OF THE UTERUS IN A MOUSE

WILLIAM H. WOGLOM, M.D.

(From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director)

Tumors of the uterus in the lower animals are not rare, though by no means so common as in man. A number of cases has been gathered together by Casper (1), Sticker (2), Murray (3), Williams (4), Wolff (5), Fox (6), and McCoy (7); these, which include fibroma, fibromyoma, myoma, papilloma, carcinoma, and sarcoma, have been found in the horse, cow, dog, pig, rhinoceros, muskrat, beaver, ground squirrel, monkey, gazelle, and six-banded armadillo.

Among laboratory animals, carcinoma of the uterus seems to be relatively common in rabbits, Wolff (5) and Woglom (8) having collected from the literature some eight cases, while Stilling and Beitzke (9) subsequently described thirty tumors in thirteen rabbits, including myoma, adenomyoma, adenoma, and adenocarcinoma.

In the rat, a transplantable uterine carcinoma has been recorded by Singer (10). The only other uterine growths in this animal, so far as the writer is aware, are the endothelioma discovered by McCoy (11), and the two fibroadenomata quoted by Bullock and Rohdenburg (12).

The mouse appears to be affected but seldom by tumors of the uterus. Haaland (13) discovered a fibromyoma in a mouse with adenocarcinoma of the breast, and two "doubtful" lesions apparently formed on the basis of an organized retained placenta; a

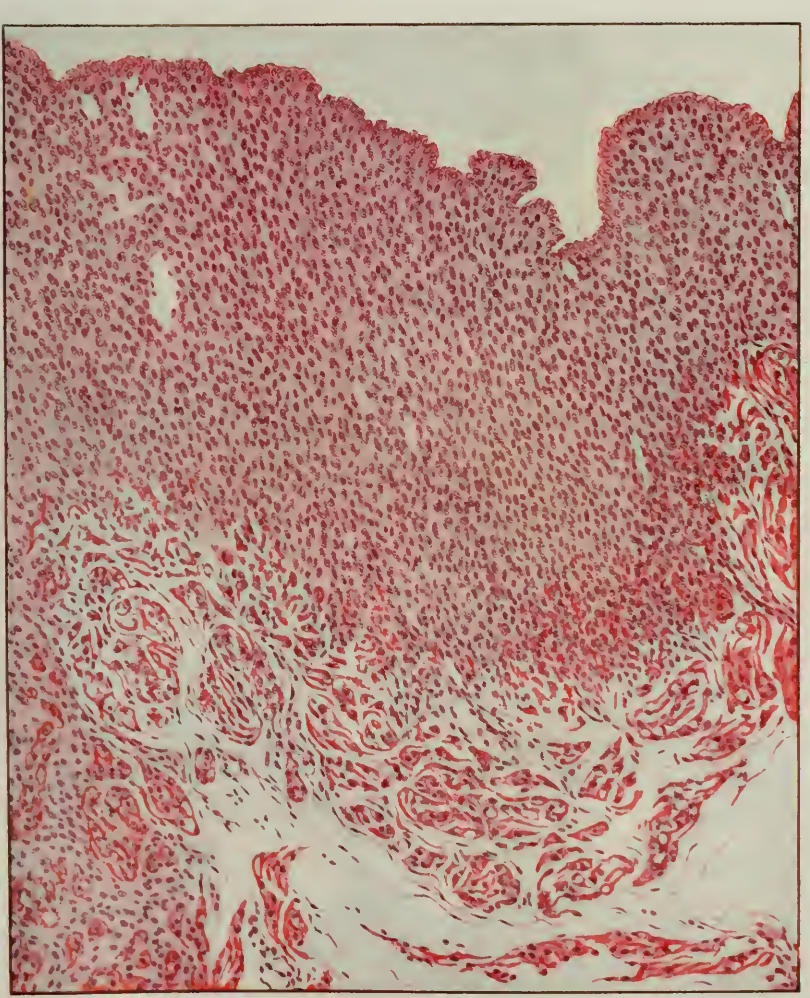


FIG. 1. Carcinoma of uterus, invading muscular wall. H. and e. × 400.

fourth resembled the case described by Tyzzer (14), where one horn of the uterus of a full-grown Japanese waltzing mouse contained a group of cysts in its wall. It was impossible to determine, however, whether this represented a congenital anomaly or a more recent development. The epithelium differed from that of the endometrium, and mitotic figures were not infrequent.

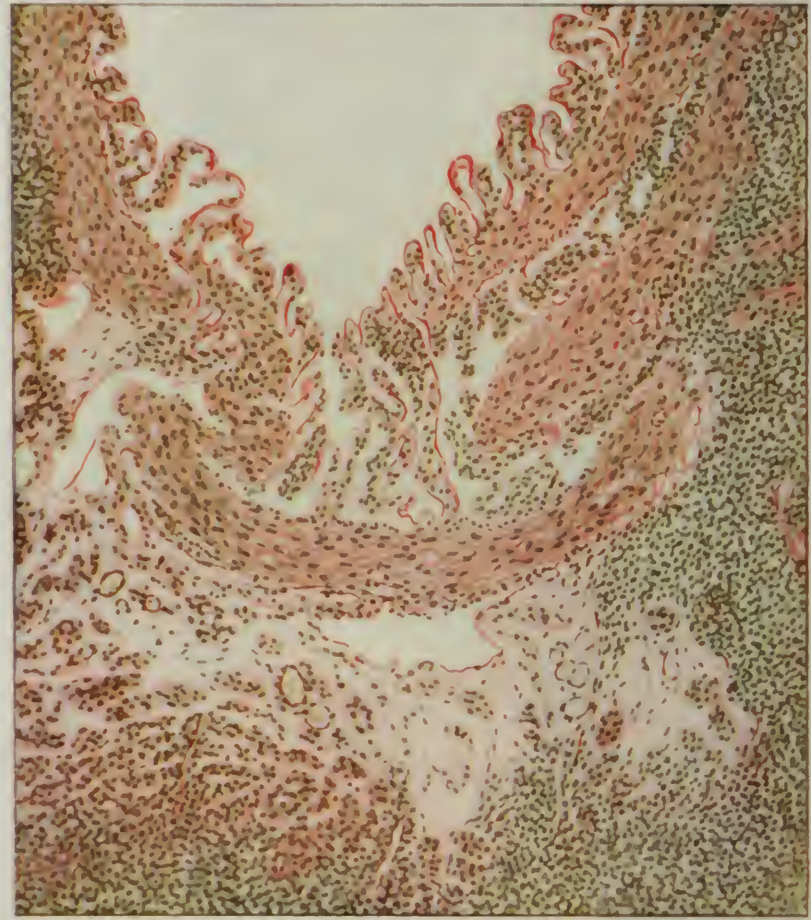


FIG. 2. Invasion of uterine wall down to peritoneal coat. Van Gieson. × 250.

The only malignant new growths of the mouse uterus that the writer has found in the literature are the four recorded by Miss Slye (15)—three sarcoma and one malignant adenoma. Hence the solid carcinoma about to be described is not without interest.

A mouse twenty-two months old, and of cancerous ancestry, was killed and autopsied November 8, 1918, because of ascites.

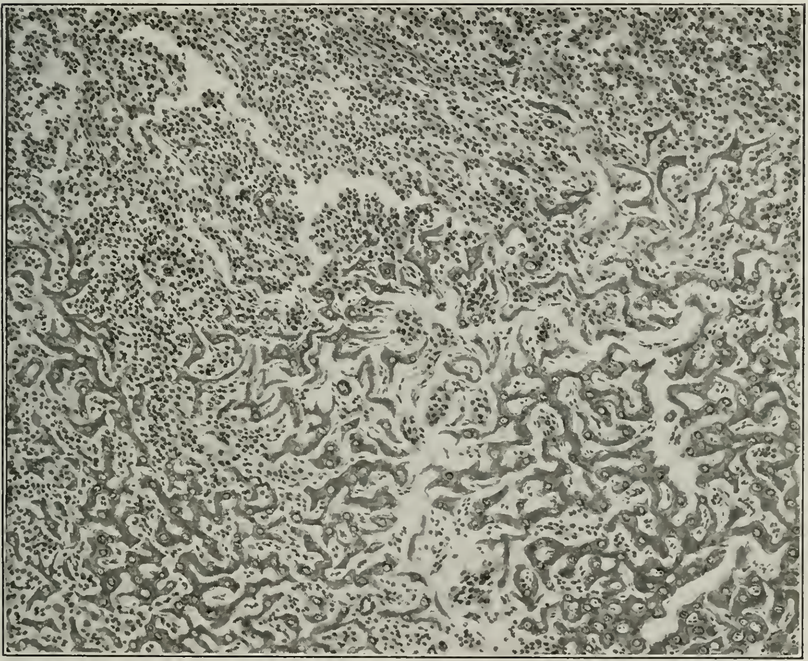


FIG. 3. Metastasis in liver. H. and e. × 230.

First noticed two days previously, this had progressed so rapidly that the mouse was now about twice her normal girth, and looked sick. At autopsy several cubic centimeters of a clear blood-stained fluid escaped from the abdominal cavity, and it was found that the right horn of the uterus was the seat of a spindle-shaped thickening, situated half way between the end of this horn and the bifurcation, and measuring about one centimeter in length and half a centimeter in width; the walls were about one quarter of a centimeter thick. The liver was studded with lenticular or spherical nodules varying from less than a millimeter to half a centi-

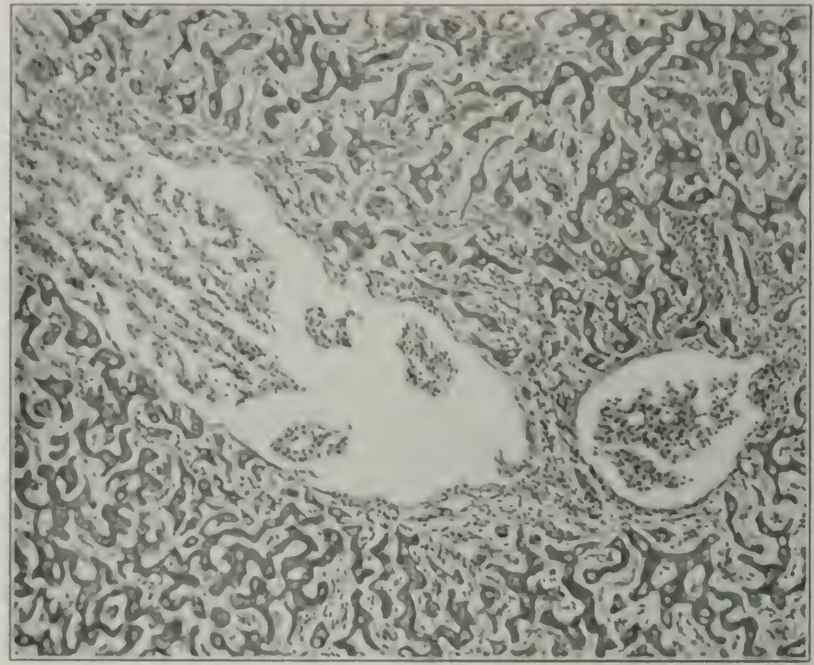


FIG. 4. Tumor emboli in hepatic vessels. The slight suggestion of glandular structure was not appreciable anywhere else, either in the primary growth or in its metastases. H. and e. × 230.

meter in diameter. The growth could not be transplanted, on account of the temporary shortage of mice in this laboratory, brought about by the war.

The microscope showed a tumor which had apparently originated in the mucosa, and which had invaded the muscular wall (Fig. 1) to the peritoneal coat (Fig. 2). The entire absence of any glandular arrangement necessitated a Bielschowsky stain, which proved the absence of connective tissue fibrils between the individual cells of the primary growth and of its metastases, and established its epithelial nature. The tumor cells were dividing freely. Fig. 2 reproduces the edge of one of the many secondary growths in the liver, and Fig. 3 shows the invasion of a blood-channel.

The cells of this growth closely resemble those of the uterine mucosa, being entirely unlike liver cells: and the presence of a multitude of nodules in the liver and of but one in the uterus is additional reason for regarding the neoplasm as primary in the uterus.

References

1. Casper: Lubarsch-Ostertag, *Ergebn. d. allg. Path.*, 1896, iii[1], 692; 1896, iii[2], 754; 1907, xi[2], 1068.
2. Sticker: *Arch. f. klin. Chir.* (Langenbeck), 1902, lxv, 616, 1023.
3. Murray: Third Sci. Report, Imperial Cancer Research Fund, London, 1908, p. 44.
4. Williams: Natural History of Cancer, New York, 1908, p. 93.
5. Wolff: Die Lehre von der Krebskrankheit, Jena, 1913, iii Teil, Erste Abt., p. 208.
6. Fox: *Jour. Path. and Bacteriol.*, 1912–13, xvii, 217.
7. McCoy: *Jour. Infect. Dis.*, 1914, xiv, 53.
8. Woglom: The Study of Experimental Cancer, New York, 1913, p. 22.
9. Stilling and Beitzke: *Virchow's Arch.*, 1913, ccxiv, 358.
10. Singer: *Jour. Path. and Bacteriol.*, 1913–14, xviii, 495.
11. McCoy: *Jour. Med. Research*, 1909, N. S. xvi, 285.
12. Bullock and Rohdenburg: *Jour. Cancer Research*, 1917, ii, 39.
13. Haaland: Fourth Sci. Report, Imperial Cancer Research Fund, London, 1911, p. 11.
14. Tyzzer: *Jour. Med. Research*, 1907–08, N. S. xii, 179.
15. Slye: *Jour. Cancer Research*, 1916, i, 479.

Discussion:

Dr. Wood: The report of all these varieties of tumors which are being discovered in animals is interesting from two points of view. One is, twenty years ago tumors of the breast in mice were regarded as rarities, and now it is only a question of what percentage of mice in a given strain will have carcinoma. The occurrence may be as high as 30 to 40 per cent. in various strains. In the second place, it is also now being shown that tumors of all varieties occur in animals, as do similar tumors of the various organs, just as in man. I have no doubt if more mice were autopsied we would have a very much larger collection of tumors of the uterus than has been so far reported. This is one of the explanations of the apparently increasing tumor rate in human beings, so that with our improved knowledge of diagnosis the number of human tumors reported in this country will probably be shown to increase slowly and ultimately reach a considerably higher rate. With our present methods of reporting deaths it is certain that at least 10 or 15 per cent. of tumors escape diagnosis. It is at least that in England, which has the best vital records. The fact that radiography of the lungs of considerable numbers of persons suspected of having tuberculosis by the physicians examining draft applicants has shown a large number of instances of carcinoma of the lung which have been classed as chronic tuberculosis is not an uninteresting point in this connection.

CONGENITAL BILATERAL STRICTURE OF THE URETER

ISIDOR MUFSON, M.D.

(From the Pathological Laboratory, Lincoln Hospital and Home, New York City)

To judge from the literature congenital stricture of the ureter is not rare, but a bilateral stricture of the ureter is a rare congenital defect, only eight cases exclusive of the one here recorded having been described. To judge from the few cases recorded these strictures are most often discovered at the extremes of life, most of them having made themselves apparent before the age of five years. Two cases have occurred in adults, one at twenty-five years, and the other at sixty-two years.

No apparent reason for this congenital anomaly presents itself in studying the development of the urinary system. The ureters are primary derivatives of the bladder, growing cephalad to meet the metanephric tissue. Their lumina appear either as a result of central absorption of the epithelial outgrowth or are present primarily in the process of their evagination from the bladder (1). The failure of these processes to be completed would give rise to the obliteration of the lumen. Another explanation rests upon an anatomical characteristic of the ureter in the embryo, namely the presence of valves. In the case reported by Watson and Cunningham (2) it is probable that the valves became adherent at their margins or lost their elasticity and so caused the narrowing of the lumen.

In the ureter there are three sites of predilection where the lumen may be obliterated, and these are at the junction of the ureter with the renal pelvis, at the brim of the bony pelvis, and at the vesical end. When the obstruction occurs at the vesical end, obliteration may occur just outside the bladder, or in the muscular coat, or at the bladder opening of the ureter. With obstruction just outside the bladder there is a cystic dilatation extending up a variable distance from the bladder while the inner surface of the viscus is negative. With the stricture in the middle coat, there is no obvious abnormality except perhaps a dimpling or a moderate pouting at the site of the ureteral opening. When the obliteration occurs at the ureteral orifice there is a cystic outpouching from the ureteral opening which may vary daily in size as in Buerger's case (3) or enlarge so that it may present at the external urethral meatus as in the cases described by Bostrom (4).

As is to be expected the narrowing of the lumen produces a back pressure which results in structural and physiological changes in the tract behind the stricture. The extent of these changes are dependent upon the degree of atresia. If obstruction is incomplete there is a dilatation of the lumen of the ureter accompanied by an hypertrophy of the wall. The renal pelvis becomes dilated and atrophy of the pyramids and renal parenchyma follows. If the atresia is complete the result is either an atrophy of disuse or an hydronephrosis, with or without a pyogenic infection. The fluid in the hydronephrotic cases as Sollman, Williams and Briggs (5) have shown possesses the characteristics of a transudate and not that of urine.

The cases occurring in the literature briefly abstracted are as follows:

1. Whipple (7): A male aged 25 years, operated upon at the age of 14 for a right-sided hydronephrosis and at the age of 25 for a left-sided pyonephrosis.

2. Welz (8): A bilateral congenital atresia at the vesical opening of the ureters with beginning double hydronephrosis occurring in an eight-months fetus.

3. Watson and Cunningham (2): Age unknown. A marked

degree of bilateral hydronephrosis due to unyielding ureteral valves.

4. Mutach (7): A male dying 30 hours after birth. Right ureter obliterated 5 cm. from the kidney. The left ureter obliterated 2 cm. above the bladder.

5. Burchard (9): Male, 62 years of age. A bilateral stricture at the vesical openings indicated by minute depressions at the tip of protrusions presenting at the normal ureteral openings in the bladder. This was probably the type where the stricture was situated in the ureter as it passed through the muscular coat of the bladder.

6. Dycherhoff (10): A male child who died one hour after birth with respiratory difficulties. The ureter was found to be patent on the right side for a distance of 3 cm. from the bladder, the left ureter being patent for 2 cm. This author states that similar cases have been reported by Hoenes and Ahlfeld.

The case reported in this paper is that of a male infant one month old who after a normal birth was brought to the hospital with the statement that it had been restless and vomiting since birth. On physical examination a marked state of malnutrition was evident. The abdomen was much distended, the superficial veins being prominent on both sides. The child was moderately jaundiced. The temperature varied from 99° F. to 100° F. After three days in the hospital the infant died.

At the autopsy, aside from the jaundice of the skin and organs, but two abnormalities were found; the first of these was that of the gall bladder. The viscus was distended with a colorless mucoid substance and the cystic duct was completely angulated upon itself so that the two limbs were parallel. They were held in this position by a vascular band containing the cystic artery. Upon cutting this band the obstruction was released and the contents of the gall bladder could be expressed into the duodenum.

The second abnormality was in the urinary system. Both kidneys were enlarged, the pelvis and calyces were dilated and the pyramids flattened. The left kidney presented several abscess pockets, the largest of which was 0.5 cm. in diameter. Both ureters were markedly dilated, measuring almost one cm. in diameter, the ureteral walls being 0.25 cm. thick. A probe could be passed through their entire course except at the vesical end where they permitted the passage of a horse hair only. The urethra was patent and the bladder showed no abnormality. The accompanying picture shows the condition better than words can describe it (Fig. 1).

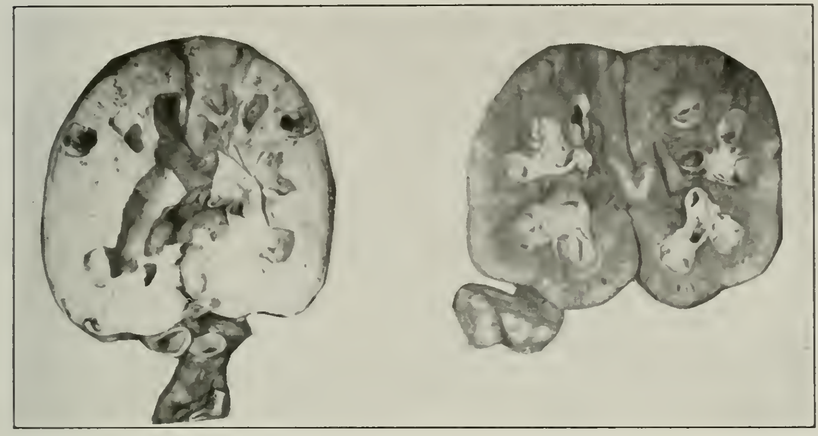


Fig. 1. Congenital stenosis of ureters showing renal lesions and diameter of ureter on section above the stricture.

References

1. Huntington: Harvey Lectures, New York, 1906–1907, 222.
2. Eisendrath: *Surg., Gynec. and Obst.,* 1911, xii, 533.
3. Bottomley: *Ann. Surg.,* 1910, lii, 597.
4. Schwarz: *Beitr. z. klin. Chir.,* 1896, xv, 159.
5. Sollman, Williams and Briggs: *Jour. Exper. Med.,* 1907, ix, 71.
6. Eisendrath: *Surg., Gynec. and Obst.,* 1911, xii, 533.
7. Cited by Welz.
8. Welz: Inaug. Diss., München, 1903.
9. Burchard: *Centralbl. f. allg. Path. u. path. Anat.,* 1896, vii, 129.
10. Dycherhoff: Inaug. Diss., Kiel, 1900.
11. Cited by Dycherhoff.

EXTENSIVE BONE FORMATION IN THE THYROID

H. WILLY MEYER, M.D.

(From the Pathological Laboratories of the Lenox Hill Hospital in the City of New York)

The specimen I am presenting to-night is from the autopsy of a man who died of influenzal pneumonia. We noticed at autopsy that he had a growth in his neck on the left side, and also that his left pupil was markedly dilated. We thought that possibly these two findings might have some relation to each other, and on further dissection we found that the mass consisted of an enlarged thyroid gland. Later in the laboratory it was found to be an adenomatous thyroid with not only deposition of lime salts within the stroma, but also extensive formation of true bone. I went through the literature and such text books as Adami, Ewing, Ziegler, MacCallum, and Aschoff, and found that such conditions are reported, but that they are very rare. The specimen shows, as well as the microscopical sections, that there is hyaline degeneration of the stroma and deposition of lime salts, with marked true bone formation within the stroma.

Discussion:

Dr. Schwarz: I saw about a year ago a carcinoma of the thyroid with extensive bone formation in the trabeculæ. There was no inflammatory process, but I do not think it can be explained in that way. I should like myself to know the explanation of the histogenesis of this bone formation in the thyroid. At that time I looked up the text-books and it was stated that this was very rare.

Dr. Moschcowitz. Some years ago in connection with studies of various forms of calcification and ossification, including five cases of ossification of the ovary, I arrived at the significant conclusion that the majority of abnormal ossifications in organs occurred in tissues that had undergone necrosis or hyaline degeneration and in which a deposition of lime had occurred. Ossification in other words occurs only in tissues that have previously been calcified. I also showed that the formation of new blood vessels was the keynote to the interpretation of the pathogenesis of ossification, and that the cellular components involved in angiogenesis are the progenitors of the cellular constituents of bone. It is very rare to find abnormal bone without evidence of ossification in the neighborhood, usually in the periphery.

In all probability this is the explanation of the bony formation in this case. The thyroid tumor was probably of long standing and was the seat of necrosis or hyaline degeneration. In this degenerated area lime was deposited, and subsequently bone. I do not think that a blastomatous or teratomatous origin is at all probable.

Dr. Strong: I reported a case of bone formation in the Fallopian tube after tuberculosis which I presume is similar in origin.

CHORIOEPITHELIOMA OF FALLOPIAN TUBE; EMBRYONAL CARCINOMA OF OVARY; CARCINOMA OF RECTUM IN BOY OF SIXTEEN

L. W. STRONG, M.D.

The chorioepithelioma of the Fallopian tube occurred in a woman who was last pregnant six years ago. She came to the hospital complaining of menstrual hemorrhage. Upon examination a small sloughing mass was found in the vagina. This proved to be chorioepithelioma and a complete hysterectomy was done, but there was rapid recurrence in the pelvis, and some clinical signs in the lung.

At autopsy a large mass was found in the parametrial tissues and there were large metastases in the liver. The lungs were studded with small embolic metastases from the veins. The interest in the tumor lies in its origin, as the uterus was not at all involved. The ovary on this side was entirely destroyed, so that one cannot say what part that might have taken in the process. Therefore it is always possible that it might have been a teratoma, though I do not believe that is likely. I suppose it would come under the head of ectopic chorioepithelioma, although I think the term ectopic chorioepithelioma is particularly used in cases in the parametrial tissues not involving the tube directly. There is nothing in the history suggesting an ectopic gestation. The uterus was rather large, but entirely free, and the mass involved the whole tube. The adnexæ on the other side were normal.

The second case is a solid carcinoma of the ovary in a girl twenty years old, and the interest lies in the particular type of ovarian carcinoma that we have here. It is a solid carcinoma, not papillary or glandular. It measures about 20 cm. in diameter. In the specimen there was a small cyst with very simple epithelium lining it. There were vesicular cells packed with very few bands of stroma. The whole tumor was made up of masses of these cells alternating with areas of necrosis and fibrin. The fimbric end of the Fallopian tube is involved, but the epithelium of the plicæ is not taking part in the process. As to the tumor itself, it appears to be an embryonal type of carcinoma, and it certainly does remind one of those cases described by Pick as being teratomata of the monelemental type where the single type of cell develops into a carcinoma. In this tumor there is no suggestion of chorioepitheliomatous nature. I simply put it down as an embryonal carcinoma.

The third case is a carcinoma of the rectum from a boy of sixteen. The central mass shows quite a solid growth of carcinoma. The case is of interest on account of the age of the patient. I believe carcinoma of the rectum has been reported in young individuals, but I do not know of any case in such a young person.

CARCINOMA OF TUBE; CARCINOMA OF OVARY

EMIL SCHWARTZ, M.D.

The ovary from this case is about three times as large as a normal ovary. It contained a small cyst, the rest of the structure was solid. It was accidentally found. On section it was seen that the solid portions had numerous small plugs of sebaceous material. Of course there was the possibility that this was a dermoid cyst, but on microscopical examination one sees that the tumor is composed of large coils of glands. The cyst is lined with a typical serous ciliated epithelium. The glandular epithelium breaks through into the stroma and appears in small solid masses which show marked metaplasia. What is difficult to explain in this case is the presence of the sebaceous contents which may be seen in the gross tumor. The only explanation I can make is that they consist of cell detritus, as there were many cells in the lumen, and hyaline material, probably derived from the epithelial cells. The tumor is very small; the entire ovary measures only about 4 × 3 × 2 cm. and there was no suspicion of a carcinoma on examination of the gross specimen.

The second specimen which I have to present is also remarkable because of the size of the primary carcinoma of the tube. A tubo-ovarian cyst was removed at the same time the surgeon operated on a chronic mastitis. The tubo-ovarian cyst contained three small carcinomata, the largest one measuring only 0.75 cm. in diameter. The mass was papillary. The question is whether this is a primary carcinoma, or whether it is an infiltrating metastasis. There is no reason why one cannot assume that it is possible for several carcinomata to be produced at the same time. The implantation metastasis is not very probable because there was free fluid in the tube, although this possibility cannot be denied. The mucosa between the papillations was absolutely free, and the wall of the tube was invaded in no portion; there was only a moderate inflammatory reaction of the muscular wall.

EOSINOPHILIC (POLYMORPHONUCLEAR) LEUKEMIA

REPORT OF A CASE WITH AUTOPSY (Abstracted)

LOUIS G. SHAPIRO, M.D.

Paterson, New Jersey

Case History: Mr. A. I. Age 48 years. First seen March 29, 1916.
Chief Complaints: Cough, weakness and loss of weight.
Family History: Irrelevant.
Venereal History: Patient denied infection.
Past History: Always well until present illness.

Present Illness. Began five years ago with constant, dull pain in right thigh on its dorsal aspect. It continued without relief for nine months and then gradually disappeared. Later he suffered from pruritus of both thighs. At about that time, he was told that he had sugar in the urine. He drank considerable water, but at no time was there increased appetite.

Throughout this entire time, the patient had cough with mucoid expectoration. There was occasional fever but no sweats and no hemoptysis. He lost considerable weight,—thirty pounds. His present weight is 148 pounds. He urinates four to six times a day.

Physical Examination: His general condition is poor. There is evident loss of weight, pallor and puffiness of the eyelids. The temperature is 99.8° and pulse 120. The skin is pale and shows numerous scratch marks. The mucous membrane of the nose is swollen and covered with crusts. A spur is present on the right side of the septum. The teeth show marked pyorrhea alveolaris. The inguinal and epitrochlear nodes are palpable, but not greatly enlarged. The other lymph nodes are not palpable. The lungs show moderate dullness over the right upper lobe with increased breath sounds and subcrepitant râles. A few râles are likewise heard over the apex of the left lung and along the left border of the heart. The lungs are otherwise negative.

The heart is not enlarged. The rate is 120 per minute, the rhythm regular. The sounds are of poor quality, but no murmurs are audible. The blood pressure is 115 mm. systolic and 75 mm. diastolic.

The abdomen is moderately enlarged. No masses are to be felt. The liver is enlarged, extending from the fourth intercostal space to three finger breadths below the costal margin. The surface of the liver is regular, soft and not tender.

The spleen is enlarged, extending from the seventh intercostal space to three finger breadths below the costal margin. It is regular and firm.

The rectum and genitalia are negative. The lower extremities show slight edema.

The urine is dark amber in color, specific gravity 1030; reaction acid; albumin, heavy trace; sugar, 0.22 per cent. present in 24-hour specimen; microscopic examination reveals a moderate number of hyaline casts.

A blood smear taken at this first examination showed the following: Central pallor of the red blood cells. Differential count: Polymorphonuclear neutrophiles 32.5 per cent.; polynuclear eosinophiles 48.5 per cent.; small lymphocytes 13 per cent.; large lymphocytes 1.5 per cent.; large mononuclears 4.5 per cent. Subsequent blood counts are recorded below.

Repeated examinations of the sputum were negative for tubercle bacilli.

The stools were frequently examined for ova because of the eosinophilia, with negative result.

Fluoroscopic examination of the chest by Dr. J. Roemer, showed diminished aeration of both apices. A plate of the chest was negative.

Subsequent Course

The patient failed slowly. He constantly complained of cough. His voice was hoarse and his throat felt dry. Examination of the larynx showed swelling of the arytenoids. There was profuse perspiration and occasional itching of the skin. Vertigo, on arising from bed and while at stool, was troublesome. Later he became quite short of breath and developed marked ascites which necessitated tapping.

He was admitted to the Paterson General Hospital nine days before his death, at which time he showed marked edema of the face, swelling of the abdomen and lower extremities.

A Wassermann test made at this time by Dr. F. R. Sandt was reported as strongly positive, ++++.

The patient died on April 19, 1917, with marked dyspnea.

Blood counts made during the time that the patient was under observation are recorded in the following table.

Blood Counts

	Mar. 29, 1916	Apr. 2, 1916	Apr. 11, 1916	May 11, 1916	Jan. 27, 1917	Mar. 8, 1917	Apr. 13, 1917
Hemoglobin (Sahli)......		85%	87%				
Red blood cells		4,746,000	4,304,000				
White blood cells		19,800	17,900	15,700	77,200	81,600	236,000
Polynuclear neutrophiles.	32.5%	20%	15%	19%	6.00%	8.0%	4%
Polynuclear basophiles ..					1.33%	.5%	1%
Polynuclear eosinophiles.	48.5%	70%	77%	58%	83.33%	86.5%	79%
Myelocytic basophiles...							1%
Myelocytic eosinophiles .					66%	3.5%	5%
Small lymphocytes......	13.0%	10%	7%	20%	1.33%	1.0%	
Large lymphocytes......	1.5%			3%	7.33%	.5%	1%
Large mononuclears.....	4.5%		1%				3%
Polynuclear leucocytes with pale blue cytoplasm resembling that of the eosinophilic cells but without the granules							6%

The Microscopic Blood Findings: The red cells showed very little change except for a diminution in number and an evident central pallor.

The white cells were characterized by a steadily increasing number of eosinophile cells throughout the entire period of observation. A moderate number of these was similar to the ordinary eosinophile cell that is seen daily. They showed a nucleus consisting usually of two lobes and occasionally of three surrounded by closely crowded eosinophilic granules which entirely concealed the underlying cytoplasm.

Innumerable other eosinophile cells contained a smaller amount of granules, frequently crowded at one end of the cell leaving a pale blue clear cytoplasm. Myelocytes were present only during the latter part of the clinical course. Fig. 1. Their highest absolute number was 11,800 per cubic millimeter in a total count of 236,000 leucocytes per cubic millimeter, six days before death. They were eosinophilic and were almost always incompletely filled with granules.

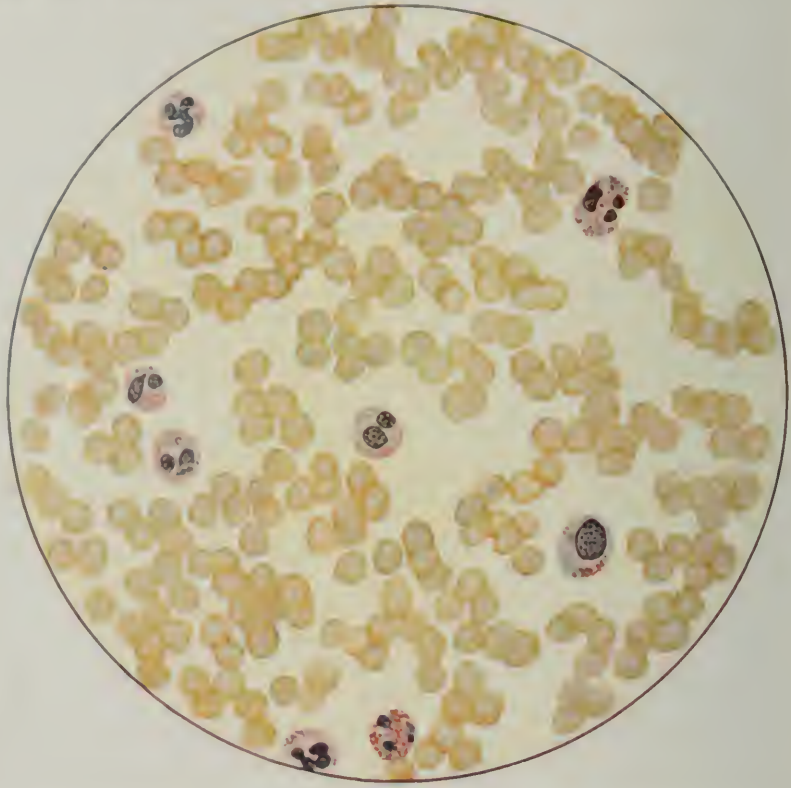


Fig. 1. The blood. Wright stain. The eosinophile cells incompletely filled with granules.

In the last blood examination made six days before death, polynuclear cells, with two lobed nuclei occurred with the same pale grayish blue cytoplasm noted above, but without any granules whatever. These apparently were very immature eosinophile cells. Their absolute number was 14,160 per cubic millimeter.

Post-mortem Findings. The autopsy was performed by me on April 20, 1917.

The body was that of a man past middle age. There was marked pallor of the face, puffiness of the eyelids, enlargement of the abdomen, and swelling of the lower extremities.

On opening the abdomen, a moderate amount of straw colored fluid escaped. The spleen was considerably enlarged and was attached by fibrous bands to the parietal wall. The liver was likewise enlarged, pale yellow and fatty. The stomach and intestines appeared to be normal. No masses were felt within the abdomen.

On opening the chest, there was no fluid in either pleural cavity. The right lung was free throughout. The surface was smooth and glistening. Its upper lobe was air-containing and crepitated. It was reddish gray on cut section, soft and elastic. No tuberculosis was found. The lower lobe of the right lung was red and congested and contained several small, brown, friable areas which appeared to be pneumonic. The left lung was attached firmly by old adhesions to the upper surface of the diaphragm. It, likewise, contained a few reddish brown friable areas in the lower lobe.

The heart did not appear to be enlarged. The pericardium was glistening and contained a normal amount of fluid. The weight of the heart was 379 gm. Its wall contained a moderate amount of fat. The right auricle was normal. In the lower part of the right ventricle there was a conical thrombus fitting into the cavity like a mould that filled its lower half (Fig. 2).

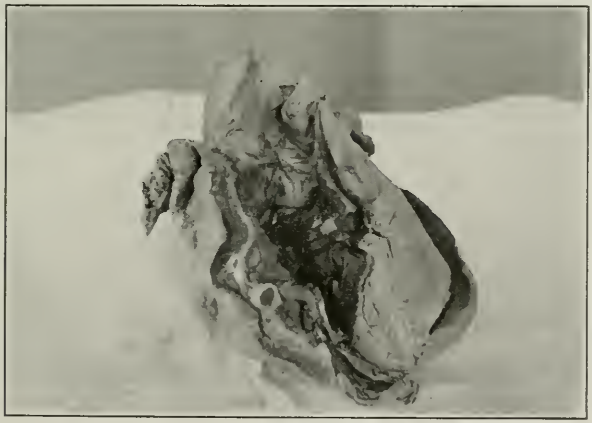


FIG. 2. The heart. Opened right ventricle and pulmonary artery presenting thrombus attached to right ventricle wall.

The greatest thickness of the thrombus was 2.5 cm. It crept up on the lateral walls of the ventricle enveloping the papillary muscles and the lower ends of the chordæ tendinæ. The mass extended into the conus arteriosus, just reaching the pulmonary valve. It did not spring from the wall of the ventricle, from which it was definitely demarcated by a white line, nor was it firmly attached except in its upper part. At the lower angle by slight traction it could be separated from the wall *en masse*. The color was greenish yellow, the deeper portion was firm in consistency. The superficial portion was crumbly and the surface appeared granular. The mass was definitely laminated and had the appearance of a thrombus. The left auricle and ventricle appeared normal. The aortic valve showed slight thickening of the semi-lunar cusps. The aorta appeared normal, no evidence of lues was present.

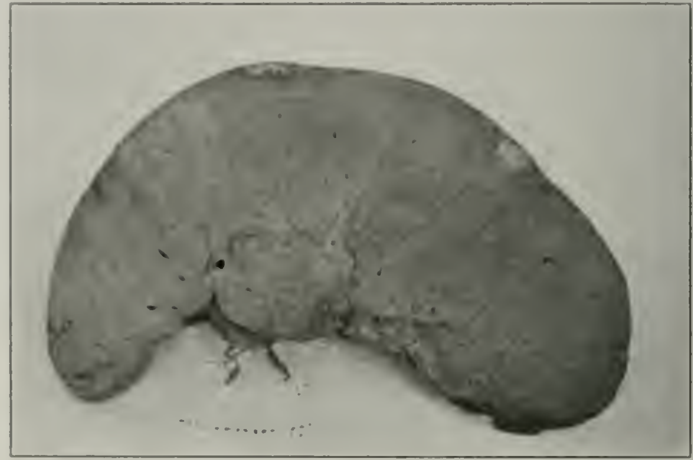


FIG. 3. The spleen. 25 × 14 × 7 cm. Weight 1,268 gm. Section showing infarcts.

The spleen (Fig. 3) was considerably enlarged. Its weight was 1,268 gms. The notching was deeply marked. It was regular, its capsule was thickened, and there were fibrous adhesions on the surface. It measured 25 × 14 × 7 cm. The surface of the spleen was dimpled by trabeculæ that extended into its substance. Small white areas could be seen through the capsule. The spleen was soft on cutting. The cut surface had a brownish red, chocolate color and was very cellular. Scattered throughout the cut surface were numerous small, white, irregular areas varying in size from 0.5 to 1 cm. in diameter. These infarcts were surrounded by a hemorrhagic zone.

The liver weighed 2,410 gms. It measured 27 × 22 × 7 cm. Its capsule was smooth and glistening. The cut surface was pale and fatty.

Both kidneys weighed 439 gms. The capsule of the left kidney stripped readily, disclosing two small, yellowish white raised spots about 3 mm. in diameter. The cut section was yellowish in color and the markings were not very clear. The cortex measured 6 mm. The surface showed several small, irregular, yellowish white areas. The right kidney had about the same appearance as the left.

The pancreas appeared normal. It was firm, but there was no evident increase in interstitial tissue.

The stomach and intestines revealed nothing on being opened. No intestinal worms were found.

The urinary bladder and prostate gland were normal.

The bone marrow was removed from the femur. There was no fat present. It cut as a solid mass and was grayish red in color.

The Microscopic Findings: The bone marrow consisted of a mass of cells. There were no fat spaces whatever. It was impossible to make out the capillary network. The predominant cells in the bone marrow were the eosinophilic myelocyte and the myeloblast. (Fig. 4.) In addition there were a few polynuclear eosinophilic leucocytes. The eosinophilic cells in the bone marrow, like those in the blood, were frequently incompletely filled with granules.

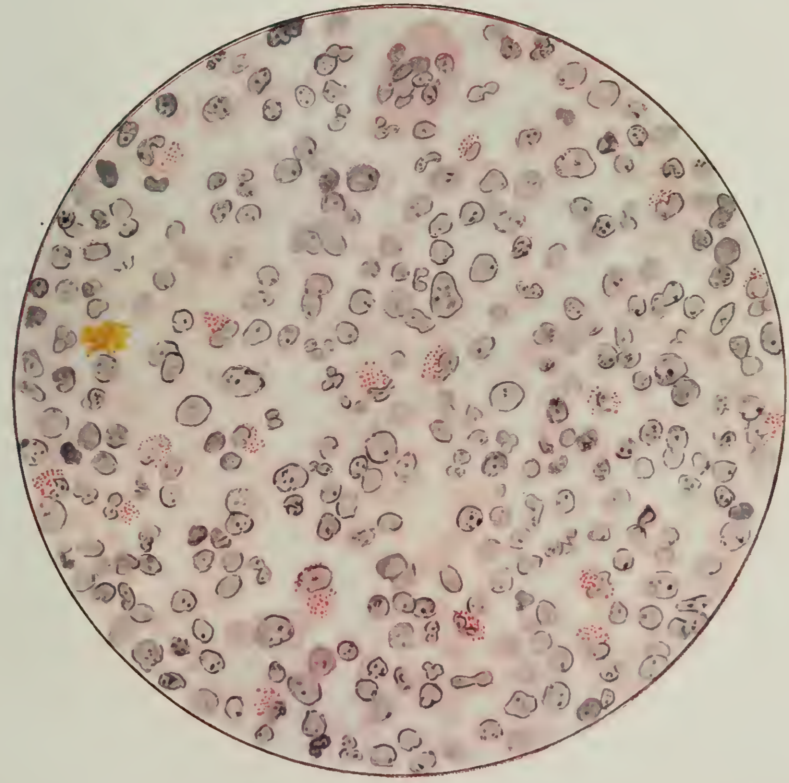


FIG. 4. The bone marrow. Hæmotoxylin eosin. Very cellular. Abundant myelocytic and polynuclear, eosinophiles. In addition, many non-granular mononuclear cells, probably myeloblasts.

The spleen showed thrombosis of vessels with infarcts. The Malpighian bodies were diminished in number. The splenic pulp was rather loosely filled with cells. Between the venules a moderate number of eosinophilic leucocytes was present (Fig. 5).

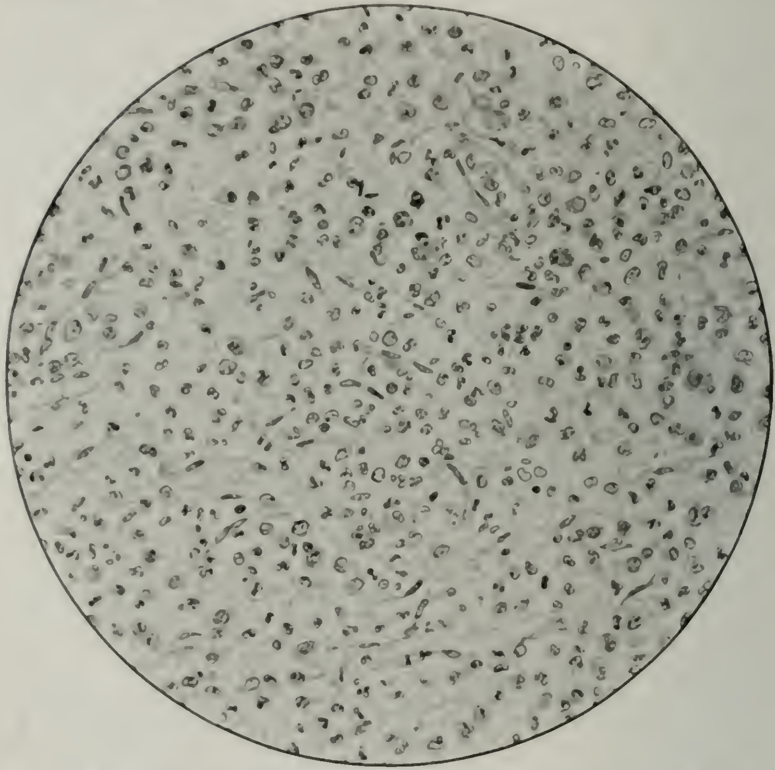


Fig. 5. The spleen. Sinuses separated by increased number of cells. Moderate number of eosinophiles.

The liver showed fatty infiltration of the liver cells and distension of the capillaries within which numerous eosinophilic cells were to be seen (Fig. 6). An occasional megalokaryocyte could be made out in the liver capillaries. Some of the liver columns appeared atrophied by the pressure of the distended capillaries filled with cells. The resulting appearance was that of foci of infiltration.

The lung showed thrombosed vessels, some of which were being canalized. Eosinophile cells were present in the larger vessels, in the capillaries and in the interalveolar septa. Heart failure cells were present in the alveoli. A section from the pneumonic part of the lung showed engorgement of the vessels in the alveolar wall and a fibrinous exudate within the alveoli which contained numerous erythrocytes and neutrophilic leucocytes, but no eosinophiles.

The heart. A section through the right ventricular wall and a part of the attached thrombus showed separation of the muscle fibers by distended capillaries which contained many eosinophile cells. The thrombus showed fairly well marked organization of its base, with deposition of considerable pigment (Fig. 7).

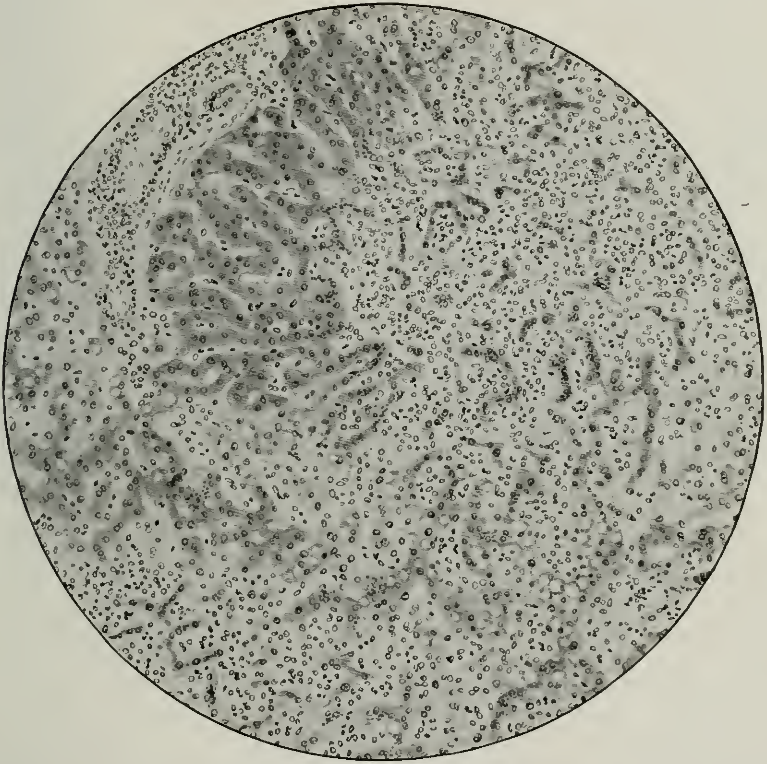


FIG. 6. The liver. Infiltration with bone marrow cells. Atrophy of liver columns.

In a review of the literature, I have been able to find one similar case recorded by H. Z. Giffin.[1] The case is noted as one of splenomegaly with marked eosinophilia, for which splenectomy was done without affecting the course of the disease.

[1] *Ann. Surg.*, 1915, lxii, 170.

The clinical history and the blood findings resemble very much those of the case reported above. The first blood count showed 15,400 leucocytes with an eosinophilia of 66 per cent. The last blood count noted was done some time after splenectomy and showed a leucocyte count of 138,000 of which 75 to 80 per cent were eosinophiles.

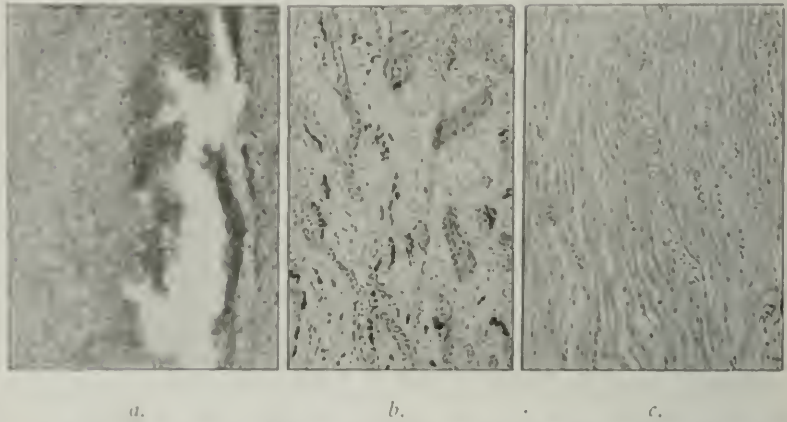


Fig. 7. The heart. Section of right ventricle and attached thrombus. *a*, fresh thrombus; *b*, portion of organized thrombus; *c*, separation of muscle fibers by distended capillaries which contain many eosinophile cells.

CONCLUSIONS

I am at a loss to know the cause of this unusual alteration in the blood. A parasitic cause could not be found. The positive Wassermann reaction I believe has no bearing, even though a moderate eosinophilia is known to occur in congenital syphilis. It seems to me that theoretically a leukemia of the eosinophile system of cells might occur provided there was the proper chemotactic agent.

In this case the clinical manifestations, weakness, loss of weight, enlargment of the liver and spleen, ascites and steadily rising white blood count, as well as the changes found post mortem, namely the cellular conversion of the bone marrow, and the infiltration of the spleen, liver and lungs with eosinophile cells and the frequent occurrence of thrombosis, are in many respects similar to the processes found in the ordinary myelogenic leukemia. I believe this is a case of leukemia arising in the eosinophilic system of cells.

Discussion:

Dr. Libman: I have nothing to add, but I want to compliment Dr. Shapiro on his careful study of the case. I was familiar with the case to which Dr. Shapiro referred, and the two cases seem very similar. There was apparently marked edema in both instances. I hope that Dr. Shapiro will give a name to this condition, because it appears to be a new clinical entity.

Dr. Ottenberg: In the ordinary myeloid leukemias all the cases have smaller and larger numbers of eosinophiles among the cells, and I am sure I have seen cases that had some predominance of these cells, although I have never seen anything like this blood picture, which is unique. The immature eosinophile cells described occur in trichinosis eosinophilia, and they do occur sometimes in the ordinary forms of leukemia.

IS THERE A PARALLELISM BETWEEN NORMAL AGGLUTININS AND HEMOLYSINS OF HUMAN BLOOD?

With Special Reference to Transfusion Tests

REUBEN OTTENBERG, M.D., AND FRANCES KRASNOW, A.M.

A year ago we were asked by the Division for Medical Sciences of the Research Council of the National Council for Defense to take up the question of whether the strength of the iso-hemolysin in human serum ran parallel to the strength of the iso-agglutinins. This problem was of practical importance because it was believed by some workers that human hemolysis only occurred in serum which had strong agglutinating power. Therefore, if one did an agglutination test of a patient's blood serum with the blood cells of the proposed donor, and only weak agglutination occurred, it would be safe to use that donor, because no hemolysis would be expected.

Our own clinical experience ran contrary to this view, but we decided to put the question to an accurate test by examining a number of sera for their hemolytic and agglutinative strength.

What we proceeded to do was to group sera according to standard clinical methods, using sera from one to three days old. The first thing done was to make preliminary tests for hemolysis as follows:

Group I sera with Groups II, III, IV cells
Group II sera with Groups III, IV cells
Group III sera with Groups II, IV cells

Controls were run using each serum with its own cells. The red sera were entirely discarded.

This was followed up by a titration of the hemolysin of each serum, which showed hemolyzing power in the preliminary tests, with the several specimens of cells which it hemolyzed. In most cases six tubes were set up containing serum diluted as follows:

1st tube contained serum undiluted
2d " " " diluted 1 : 2
3d " " " " 1 : 4
4th " " " " 1 : 8
5th " " " " 1 : 16
6th " " " " 1 : 32

In some cases two additional tubes were set up with the serum diluted 1 : 64 and 1 : 128. The amount of serum used in each test was twice the amount of 5 per cent. cell emulsion. The readings of the reactions were made after (*a*) one hour incubation at 37° C. water bath; (*b*) eighteen hours in the ice box. Finally agglutinin titrations were set up for all the sera that showed hemolysis. Sera with strong hemolysis were inactivated prior to this titration.

TABLE I

(Showing Strength of Hemolysin Corresponding to WEAK Agglutinin)

Test No.	Titration of Agglutinin		Titration of Hemolysin in					
			Sera Showing Strong Reaction			Sera Showing Weak Reaction		
	Highest Dilution Showing Agglutination	Strength of Reaction in this Dilution	Undiluted Serum	Highest Dilution Giving Hemolysis	Strength of Reaction in this Dilution	Undiluted Serum	Highest Dilution Giving Hemolysis	Strength of Reaction in this Dilution
1	1:8	+	++	—	—			
26	1:16	+	+++	—	—			
27	1:16	+	+++	—	—			
28	1:32	±	+++	—	—			
218	"	±	++++	1:4	++			
276	"	±	+++	"	±			
334	"	+	+++	1:2	+++			
433	"	+	++	"	++			
435	"	+	+++	"	+++			
287	"	+	+++	—	—			
290	"	+	+++	1:2	++			
292	1:4	++				+	—	—
300	1:4	+				+	—	—
40	1:8	++				+	1:2	+
55	"	+++				+	1:2	+
302	"	+				+	"	±
303	"	+				+	"	±
304	"	±				+	—	
54	1:16	±				+	1:2	±
29	1:32	±				+	—	—
53	"	±				+	1:2	±
56	"	±				+	"	±
58	"	±				+	"	±
307	"	±				+	—	—
308	"	±				±	—	—

Weak agglutination = agglutination not marked in serum diluted 1 : 32.
Strong hemolysis = hemolysis marked in undiluted serum.
Weak hemolysis = hemolysis less than ++ in undiluted serum.
+ = Weak agglutination or hemolysis.
++++ = very strong agglutination or complete hemolysis.
++ and +++ = intermediate grades.
± = A trace of hemolysis or very feeble agglutination.

TABLE II

(Showing Strength of Hemolysin Corresponding to STRONG Agglutinin)

Strong agglutination = agglutination marked in serum diluted 1:32, or above.

Test No.	Titration of Agglutinin		Titration of Hemolysin in					
			Sera Showing Strong Reaction			Sera Showing Weak Reaction		
	Highest Dilution Showing Agglutination	Strength of Reaction	Undiluted Serum	Highest Dilution Giving Hemolysis	Strength of Reaction	Undiluted Serum	Highest Dilution Giving Hemolysis	Strength of Reaction
8	1:32	++	+++	1:2	++			
10	"	++	++++	"	++			
16	"	+++	++	—	—			
35	"	++	++	1:2	+			
36	"	++	++	"	+			
37	"	++	++	"	+			
38	"	++	++	"	++			
273	"	++	++++	1:8	±			
343	"	++	++	1:2	++			
344	"	++	++	"	++			
418	"	++	+++	—	—			
436	"	++	++	1:2	++			
217	1:64	+++	++++	1:4	++			
221	"	++	+++	"	±			
275	"	+++	+++	1:8	±			
283	"	+++	+++	1:4	+			
284	"	++	++++	"	+			
286	"	+++	+++	"	++			
348	1:128	++	+++	1:2	+			
437	"	±	+++	"	+			
324	"	+++				+	—	—
326	"	+++				+	—	—
342	"	+++				+	—	—
329	1:32	+++				+	—	—

CONCLUSIONS

In all, 76 sera were used. The various combinations of sera with cells of incompatible groups made necessary 450 separate tests; 49 of these showed both agglutination and hemolysis. As to the parallelism in the strength of the two, a tabulation of the results (Tables I and II), shows that (*a*) 25 sera possessed weak agglutinating power; of these 11 showed strong hemolytic power and 14 showed weak hemolytic power; (*b*) 24 sera gave strong agglutination reactions; 20 showed strong hemolysis; 4 showed weak hemolysis. It is worth noticing this finding: 3 of these 4 sera with weak hemolysis showed very marked agglutination in 1 : 128 dilution (+ + +) and one showed very marked agglutination in 1 : 32 dilution (+ + +). Strong and weak sera were found belonging to the first, second, and third iso-groups, and no special attention is paid to this in the Chart.

So far as can be judged from these observations, strong hemolysis accompanies strong agglutination more often than weak agglutination; and weak hemolysis parallels weak agglutination more often than it does strong agglutination. On the other hand it is not safe to conclude, because agglutination is weak, that hemolysis will not occur. Strong hemolysis often occurs with weak agglutination. In the practise of transfusion, therefore, donors should be rejected whose red cells would be agglutinated by the patient's serum, whether such agglutination be weak or strong. Any such case provides the possibility of extensive hemolysis occurring in the body.

Proceedings
of the
New York Pathological Society

New Series, Vol. XIX OCTOBER–DECEMBER, 1919 Nos. 6-8

CONTENTS

PAGE

Two Cases of Myxo-lipo-sarcoma, Retroperitoneal. *L. C. Knox, M.D.* ... 90
The Pathology of the Poisonous Gases Used in the War. *Alwin M. Pappenheimer, M.D.* ... 97
A Case of Carcino-Sarcoma of the Breast. *A. O. Wilensky, M.D.* ... 113
A Case of Giant Celled Sarcoma of the Breast. *D. S. D. Jessup, M.D.* ... 117
A Clinical Classification of Nephritis Based on Pathological Findings. *J. Levy, M.D.* ... 121
Cysticercus of the Fourth Ventricle. *Leo Loewe, M.D.* ... 127
Periarteritis Nodosa. *George Baehr, M.D.* ... 131
Digestive Capacity of Splenic Adult Mesenchyme as Factor in Tumor Destruction. *Vera Danchakoff, M.D.* ... 136
Diffuse Carcinoma of Stomach. *L. C. Knox, M.D.* ... 143
Primary Intestinal Tuberculosis. *Max Palinsky, M.D.* ... 149
A Case of Thymoma. *M. Klingenstein, M.D.* ... 151
A Case of Thymoma. *James Ewing, M.D.* ... 156
An Unusual Case of Diaphragmatic Hernia; A Case of Acute Pancreatitis, due to Calculus in Ampulla of Vater. *H. F. Pohlman, M.D.* ... 160
An Unusual Case of Sarcoma of the Stomach. *Gustav A. Pagenstecher, M.D.* ... 163
Three Unusual Connective Tissue Tumors of the Breast. *Elise L'Esperance, M.D.* ... 165

TWO CASES OF MYXO-LIPO-SARCOMA, RETROPERITONEAL

L. C. KNOX, M.D.

The two tumors under consideration are not of course really unique, but at the same time are perhaps less frequent than the books on either pathology or surgery would lead one to suppose. Of course many more have occurred than have ever been reported, as only about 25 are mentioned in the literature. Probably at least three times that number are reported in situations other than retroperitoneal.

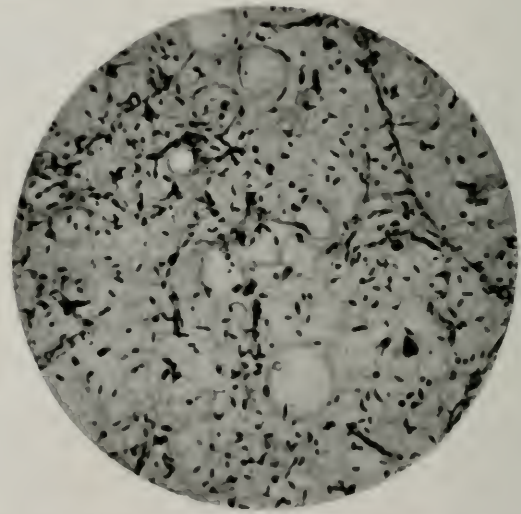


Fig. 1. Case A. P. Myxo-sarcoma containing a few fat cells.

Besides their infrequency an interesting surgical consideration is also the fact that occurring relatively well encapsulated and being therefore fairly easily enucleated, they are prone to appear clinically as much less malignant than their course has frequently shown them to be.

The first tumor occurred in a patient, A. P., admitted to St. Luke's Hospital on the service of Dr. Walton Martin in September, 1918. She was an Italian woman, housewife, aged 28. Her

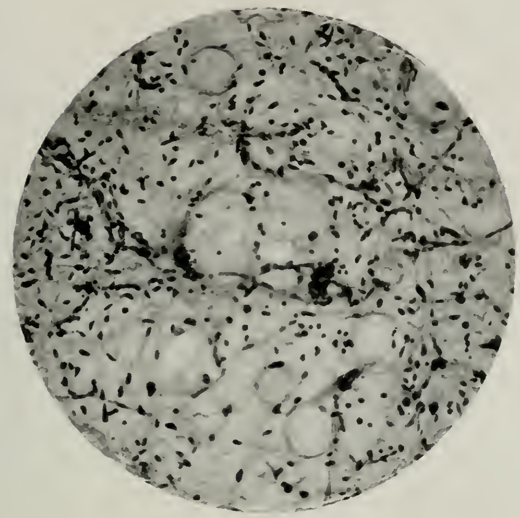


FIG. 2. Case A. P., showing variations in size of nuclei and delicate endothelial vessels.

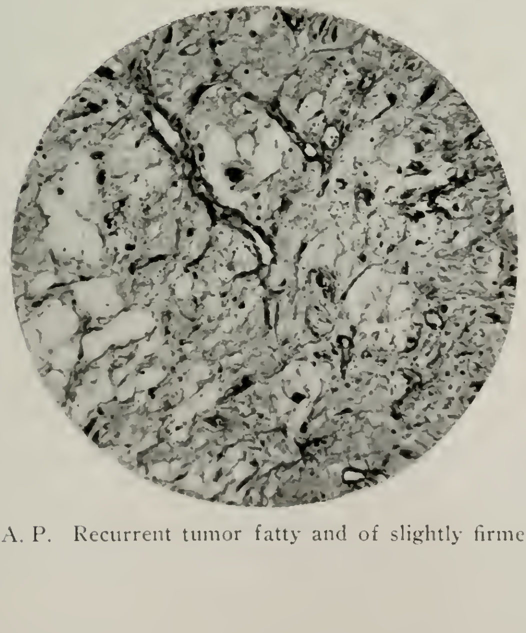


FIG. 3. Case A. P. Recurrent tumor fatty and of slightly firmer consistency.

chief complaint was of an abdominal mass; duration four months.

Present Illness.—Had suffered no inconvenience except the presence of the mass and the associated enlargement of the abdomen.

Past History.—Had been operated $1\frac{1}{2}$ years before at the Italian Hospital for an abdominal tumor (no further data regarding this have been obtainable).

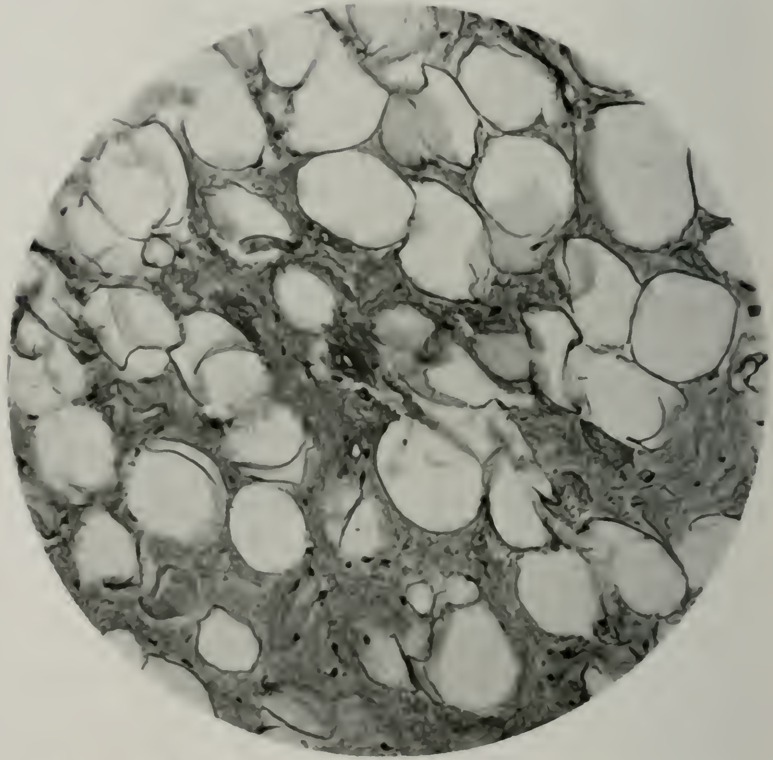


Fig. 4. Case B. H. Portion of tumor in which lipoma predominates.

Four months before admission to the hospital gave birth to a normal child and following the puerperium the present mass was noted. There was no pain, fever, loss of weight, urinary or digestive symptoms.

Physical examination showed a patient appearing chronically ill. Head, neck and thorax normal. Abdomen was soft with a large movable mass palpable in the upper left quadrant. Two parts were distinguishable, the upper the size of a kidney, the lower twice its size. Pelvic examination negative.

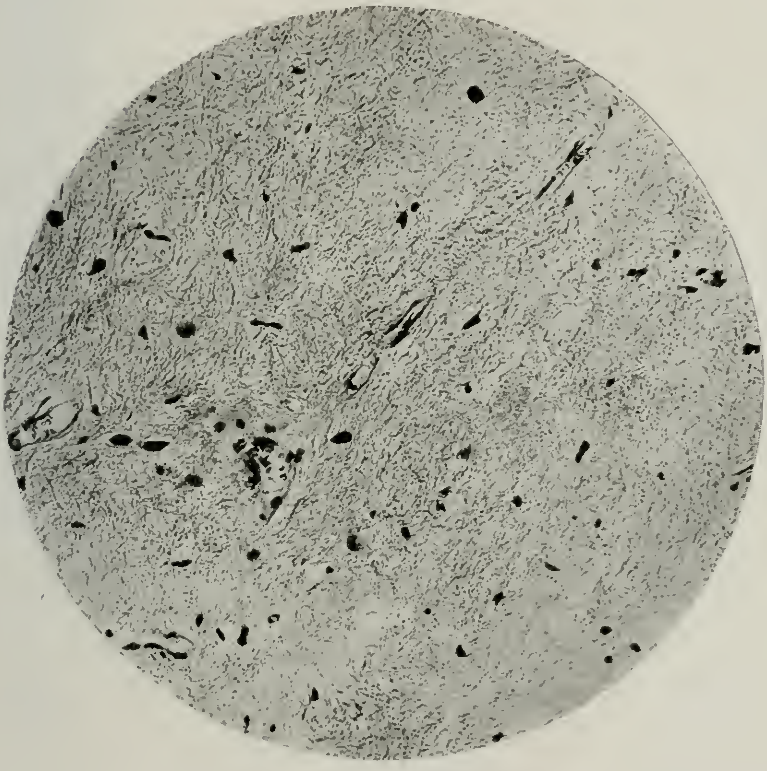


FIG. 5. Case B. H., showing myxomatous area and vascularity.

Laparotomy was done on September 12, 1918, when the large, soft, kidney-shaped tumor was found below the lower pole of the left kidney. It was easily extirpated and the patient made an uneventful recovery.

On January 6, 1919, one year and four months after the first operation, the patient returned complaining of another abdominal mass.

She was again operated upon and the second specimen, somewhat larger than the first, more vascular and more lobulated, was removed from the left lumbar region. Recovery was again satisfactory.

Soon after leaving the hospital, *x*-ray treatments were begun and have been continued at about fourteen-day intervals since.

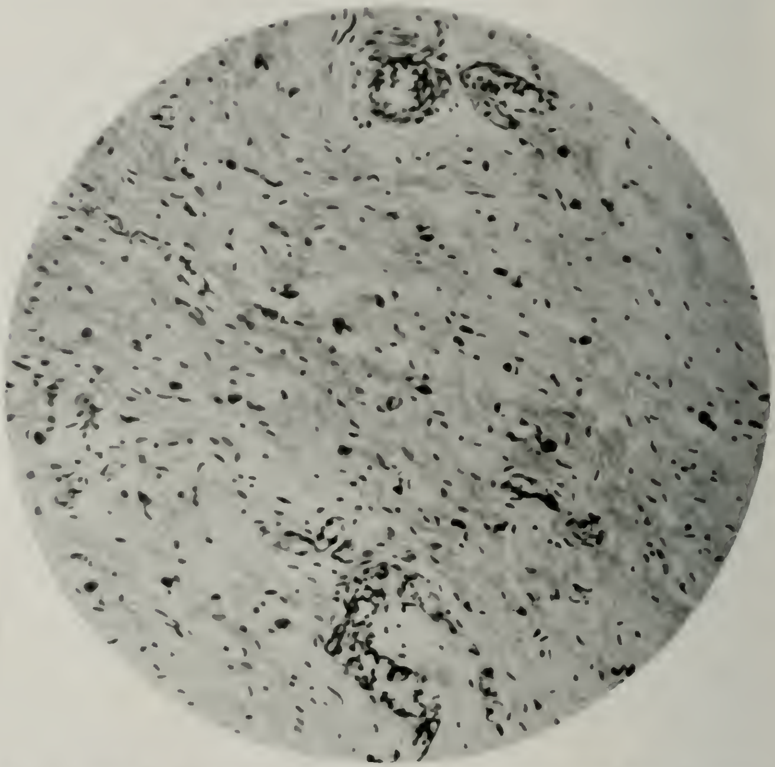


FIG. 6. Case B. H. Myxo-sarcoma. The nuclei are relatively infrequent, but irregular and hyperchromatic.

In about six months, however, a left abdominal tumor again became palpable, as it is at the present time. The patient's general condition is, however, very good.

The second case, B. H., a woman of 55, was also admitted to Dr Martin's service in September, 1918. Her chief complaint was an abdominal tumor.

Present Illness.—Patient has noted a mass in her left side for several years. Thinks it has diminished in size at times. Occasionally has felt dull pain in this area. For three days prior to admission, it has been sharp. Has lost 15 pounds in three months.

Other history irrelevant.

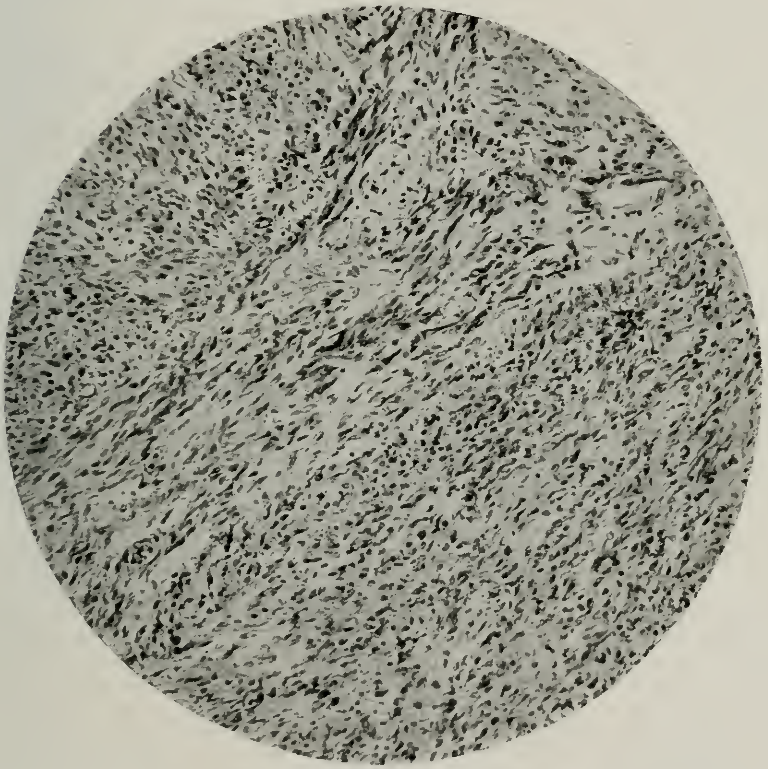


Fig. 7. Case B. H., showing an area of spindle-celled fibro-sarcoma.

Physical Examination.—Patient appeared in good health; normal except for a mass the size of a child's head in the left lower abdomen.

Laparotomy was done and the large tumor was found retroperitoneally below the lower pole of the left kidney. It was removed through the anterior abdominal incision. Recovery was uneventful.

In February, 1919, five months later, the patient returned with a recurrence. This took the form of a hard mass in the left lower quadrant extending to the crest of the ilium. It was not tender nor fluctuating. At operation there was found a large retroperitoneal mass involving the left side of the pelvis and iliac fossa. The mass was stony-hard, so that only a fragment which was more or less discrete, could be removed even for examination.

The patient recovered and left the hospital, but the prognosis appeared unfavorable.

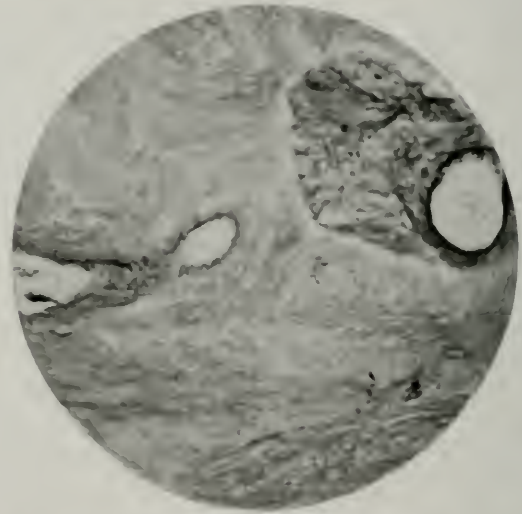


FIG. 8. Case B. H., showing ossified portion of tumor.

Sections of the tumor from the first case, A. P., show fat and various forms of fibrous tissue and true myxoma. Large multinucleated cells are frequent (Figs. 1 and 2).

The recurrence is of the same type, although slightly firmer and more fibrous, but still is distinctly cellular (Fig. 3).

The second tumor, from B. H., shows that the large nodular masses vary considerably, part being almost entirely fatty (Fig. 4), others myxomatous (Figs. 5 and 6), while the fibrous tissue is very compact and resembles a fibro-sarcoma (Fig. 7). A hard, round, ossified portion was without periosteum and found embedded in the fibrous tissue (Fig. 8).

The small rounded fragment from the second operation is intensely hard and apparently ossified.

References

ROBERTSON: *Jour. Med. Research*, 1916, N. S., xxx, 131.
RIBBERT: *Frankfurter Ztschr. f. Path.*, 1910, iv, 30.
WALDEYER: *Virchow's Arch. f. path. Anat.*, 1864, Bd. 32, 543.
VOECKLER: *Deutsch. Ztschr. f. Chir.*, 1909, xcviii, 149.
BULL: *Norsk Mag. f. Lægevidensk*, 1919, lxxx, 145.
VAN LEEWEN: *Nederl Tipdsch v. Geneesk Amst.*, 1915, i, 434.

THE PATHOLOGY OF THE POISONOUS GASES USED IN THE WAR

ALWIN M. PAPPENHEIMER, M.D.

The desirability of having a systematic examination made of the fatal cases of poisoning by the toxic gases used against our troops was early recognized by the Chemical Warfare Service, as well as by the Medical Corps. Major H. C. Clark was appointed chief pathologist to the C. W. S., and through his efforts a well-equipped pathological laboratory was installed at the experimental field of the C. W. S. near Chaumont. Major C. B. Farr, Captain Vance and the writer were assigned by the Medical Corps to assist in the work. A physiological laboratory under Major Richards, and a chemical laboratory under Captain Crenshaw, cooperated in the experimental field work.

It was hoped that, with the aid of specially designated pathologists at various field, evacuation and base hospitals, much material might be collected for study, and a close watch maintained for lesions caused by new gases, should the enemy introduce them into use. The value of the French Centres Medico-légaux in maintaining a constant vigilance for the detection of new types of gas, and in disseminating information as to the gases in use, had already been demonstrated.

These expectations were only in part realized. Transportation difficulties, impossibility of obtaining accurate data as to the nature of the gas attack, imperfect liaison with the regimental or divisional gas officers, on the one hand, and with clinical officers on the other, made the collection of material difficult, and its study of lesser value from the practical viewpoint. Had the war lasted, the organization and usefulness of the laboratory would undoubtedly have been greatly bettered.

During the short period in which the laboratory was actively functionating, we succeeded in obtaining material from 69 cases of death due to exposure to gas. These, and some 13 additional cases collected from other sources form the basis of this preliminary report.[1] Lieut.-Col. Clark, Major Jean Oliver and the writer are still engaged in a study of the pathology of the war gases, and hope eventually to acquire data for a comprehensive report.[2]

Of these 82 fatal cases, 74 have been diagnosed as due to dichlorethyl sulphide; 5 to suffocant gases, such as phosgene, diphosgene or chloropicrin; in three cases the diagnosis remains in doubt. Whether these figures are representative of the total distribution of fatalities due to vesicant or asphyxiating gases in the A. E. F., I am unable to state. Many of the cases due to phosgene and the other gases of this type, died in forward areas where autopsies could not be performed, or where the preservation of material for subsequent transport to the Central Laboratory was impossible; whereas the "mustard cases," survived until they reached the evacuation or base hospitals. It is probable, therefore, that our material does not accurately reflect the proper proportion between the two types of gases.

---

[1] Since this report was written, material from additional cases has been received, bringing the total up to 116 cases.

[2] The autopsies on the cases covered by this report were performed by the following pathologists, to whom we are indebted for material and for notes on the clinical features, and gross lesions: Major Rolfe Floyd, Major Daniel Glomset, Capt. J. F. Coupal, Capt. Jean Oliver, Capt. Robert Benson, Capt. B. S. Kline, Capt. M. Flexner, Capt. C. B. Coulter, Capt. B. F. Weems, Lieut. R. M. Wilder, Lieut. H. E. Schoonover, Lieut. Perry J. Manheims and Lieut. H. H. Robinson.

1. *Pathology of the Arsine Compounds.*—In spite of the extensive experimental work done here and abroad upon the toxicity of the solid and gaseous arsine-halogen compounds, and in spite of the known use of these substances by the Germans, either alone or in combination with the suffocant gases, there seems to be little evidence that in actual field concentration they ever brought about fatal casualties. It is true that Kling and others have succeeded, in a few cases, in extracting arsenic in fair quantity from the lungs after death, and that arsenic has been recovered from the urine during life. This, however, proved only that the arsenical gases were inhaled and absorbed, not that they were the cause of the cutaneous or respiratory lesions. Pathologically, no distinctive features have been found to differentiate these cases from those caused by the more familiar gases, and since they were commonly combined with or followed by phosgene or diphosgene, it was difficult or impossible to estimate the part played by them in the production of the lesions.

2. *The Pathology of Poisoning by Dichlorethyl Sulphide.*—There are certain features in the action of this peculiar vesicant that have aroused particular interest, and that distinguish it from the usual chemical irritant. The definite existence of a latent period up to four to six hours—the persistence of its action—the variations in individual susceptibility, and the apparent development of hypersensitiveness upon repeated exposure—these and other features have made the study of this substance interesting, apart from its great practical importance in the war. The work of R. Lillie, Clowes and Chambers,[1] confirming the theory of Marshall, Lynch and Smith,[2] supports the idea that dichlorethyl sulphide penetrating the cell by virtue of its high lipoid solubility, produces cytolysis by becoming hydrolyzed within the cell, thus liberating free hydrochloric acid after the normal buffer action of the cell protoplasm is exhausted. The low toxicity of the other products of hydrolysis has been demonstrated. This mode of action would explain the latent period and the persistency of its action. The variations in individual and species susceptibility, and the problem of acquired sensibility, have also been the subject of experimental investigation.

The pathological alterations produced in the eyes, skin and respiratory tract are now well known. The studies of Mackenzie,[3] of Winternitz[4] and his co-workers, of Warthin and Weller,[5] in this country, of the Chemical Warfare Committee[6] in England, and of Mayer, Fauret-Frémet[7] and others at the Collége de France in Paris, have pointed out the salient features in the pathology of mustard gas poisoning. I shall have few original observations to add from a study of our material.

(*a*) *Cutaneous Lesions.*—The cutaneous effects may be summarized as erythema, followed often by pigmentation and vesication. The common sites for the burns are the face (especially the scalp), eyelids, nose and lips, the neck, elbows (from lying down on contaminated ground), the scrotum and the under surface of the penis, the inner surface of the thighs, the buttocks, and the hands and feet. The size of the vesicles varies from minute sudamina-like lesions to large bulke a foot or more in diameter. The contents of the vesicles are at first clear, later they may become slightly turbid, and may show a loose coagulum. They do not become frankly purulent, unless they are infected.

In severe burns the superficial portion of the corium may be involved in the necrosis.

Histologically, a study of small early lesions shows that the vesicles may form at various levels of the skin—in the epidermis itself by hydropic swelling, dissociation of the cells and subsequent cytolysis; or in the superficial portion of the corium, elevating the entire epidermis. The dead epidermis, in small lesions, may persist until new epithelium, growing out from the margin, or from the sheaths of the hair follicles, creeps over the base of the vesicle. Aside from an initial hyperemia, there is very little inflammatory reaction. The few leucocytes that wander to the surface become pycnotic and fragmented. I have not been impressed with the severity of the vascular injury, and am not inclined to regard the relatively trivial lesions of the blood vessels as the prime cause for the delayed healing. Thrombi are not often found at any stage of the process, and it seems more probable that it is the persistence of the toxic agent within the cells of the corium and epidermis that slows the reparative process.

The statement has been made that the contents of the vesicles contain sufficient of the toxic material to cause new vesicles in other parts of the body, or even to produce lesions in another person upon contact. Experiments by Warthin and Weller, Majors Clark and Richards[8] and others show convincingly that such is not the case. The serum of the vesicles is quite devoid of vesicant action.

Very interesting is the group of cases showing a diffuse and intense brownish pigmentation which may involve almost the entire body and be unaccompanied by vesicle formation. Such cases, even in the absence of respiratory infections, may show an extreme asthenia and apathy, a low blood pressure and curious mental symptoms. The clinical picture has suggested to some of the French observers (Satier and Gaos[9]) an acute adrenal insufficiency, but definite evidence in favor of such a theory is lacking. It would have been interesting to make a careful histological study of the adrenals in a series of such cases, but our material was of little value for the purpose.

(*b*) *Lesions of the Respiratory Tract.*—Coming now to the lesions of the respiratory tract, we find a wide diversity in different cases. These differences depend in part doubtless upon the varying concentration of the gas, as well as the varying duration of the exposure. Definite data as to these factors were rarely obtainable. But the variations depend also upon the character and intensity of the secondary infection which inevitably follows upon the chemical injury; and, indeed, in a study of the finer changes, one is constantly puzzled to decide what lesions are to be attributed to the gas and what to the bacterial agents. It not infrequently happened that mildly gassed individuals, after transfer to a base hospital, contracted fatal influenzal pneumonia, and the anatomical findings in such cases may differ in no essential respect from primary cases of influenzal pneumonia.

In spite of these reservations and of exceptional cases in which the diagnosis remains uncertain, it is possible to describe a fairly definite anatomical picture. In practice, it was most unusual to find severe respiratory lesions without ocular or cutaneous lesions, especially the matted crusts on the under surface of the penis and the contiguous scrotal surface.

Lesions of the tongue are not often described. The upper part of the pharynx, the epiglottis, the trachea and the larger bronchi inevitably show the effect of the irritant, but the lesions vary from a simple hyperemia, often with punctate or larger hemorrhages to an intense diphtheritic inflammation, in which the respiratory passages from the larynx down to the smaller bronchi are lined with a more or less adherent grayish membrane.

Histologically, one obtains pictures showing every grade of severity. In the mildest cases, there is necrosis merely of the superficial epithelium, leaving one or more rows of cells intact, and still attached to the basement membrane. More commonly, the entire surface epithelium is necrotic and exfoliated *en masse*, the cell debris entering into the formation of a more or less definite fibrino-purulent membrane. The subepithelial tissue is also involved to a variable degree. In some instances, the swollen membrana propria persists, and the underlying connective tissue (though œdematous and infiltrated with leucocytes, red blood cells and fibrin) remains alive. In other cases the coagulative necrosis extends to the mucous glands. These differences appear to depend rather upon the initial severity of the injury than upon the length of time which has elapsed before the patient succumbs.

There are several histological details which deserve mention. The leucocytes, chiefly polynuclears which wander towards the surface in the early stages of the injury, show pycnosis and fragmentation—and this is unquestionably more marked and constant than in simple bacterial infections. Knowing from our experimental studies the specific leucotoxic effect of the dichlorethylsulphide when injected intravenously into animals, it seems reasonable to ascribe the leucocytic destruction to the direct action of the chemical rather than to the bacterial infection. The bacteria, moreover, rarely invade the subepithelial tissues in the early stages, although masses of bacteria are always found on the free surface.

Regenerative changes in the trachea and bronchi are frequently found, at times within a few days after gassing. The epithelium of the ducts of the mucous glands, which usually escapes complete destruction, sprouts out as flattened sheets over the contiguous surface, creeping along beneath the still attached membrane. Groups of surface cells, which have survived the initial injury, may also proliferate and aid in attempting to restore the epithelial surface. Whether, if the patient had survived, the trachea or bronchus would have become completely reinvested in this way, cannot be definitely stated. In one of our cases (229) we find the trachea lined after seven days with multiple layers of squamous cells, showing intercellular fibrils; the superficial row of cells is flattened, non-ciliated, and there are numerous mitoses at all levels. In this case, the regeneration is so complete that it seems probable that only the superficial cells were destroyed.

It would be of the greatest interest to know whether the metaplasia of ciliated into squamous epithelium, which so frequently accompanies repair in trachea and bronchi, is a permanent alteration. If so, it cannot be a matter of indifference. The loss of the normal ciliary current must predispose to bacterial infection in the lungs. Perhaps a study of late material, should we be so fortunate as to obtain it, will answer this point.

The medium-sized and smaller bronchi are quite regularly affected, very much as are the upper respiratory passages, but occasionally it happens that the necrotizing process stops short at the second or third branching, and that the terminal bronchi are found to be lined with a smooth well-preserved epithelium. Commonly, even the terminal bronchioles are found at autopsy plugged with a yellow fibrinous plug, or with a softer purulent exudate.

Histologically, one finds the same variations in the intensity of the lesions as in the trachea. At times a diphtheritic membrane of well-formed laminæ of fibrin rests loosely upon the necrotic lining of the bronchus. In other cases, the lumen is filled with a simple purulent exudate; the epithelial cells may be exfoliated and lie loose in the exudate, or they may have completely disappeared. In later cases, partial reinvestment with flattened, non-ciliated cells is the rule.

The bronchial wall is œdematous and infiltrated with inflammatory cells. Very early in some cases, fibroblasts proliferate, new blood vessels are formed, and the wall of the bronchus takes on the character of granulation tissue. It is particularly in such cases, in which the destruction of the epithelium has been complete, that we should look for great thickening, stenosis and bronchiectatic dilatation. Undoubtedly the contraction of this new-formed fibrous tissue, as well as the organization of the blood and fibrinous exudate in the surrounding alveoli, and in some cases also, the organization of the exudate within the bronchioles must lead to narrowing, if not total occlusion of many of the smaller bronchi.

In several of our cases, the trachea and bronchi have shown a foul-smelling greenish, gangrenous inflammation, and in at least one instance (case of Dr. Kline) this was associated with dental caries and spirochætal gingivitis.

Lungs.—The lungs show a bewildering variety of gross and microscopic lesions, and an attempt to analyze the material upon an anatomical basis is not very profitable. We have in our series lungs conforming to all the various types described in the recent papers on the war pneumonias, here and abroad. In a general way, we may distinguish:

1. Cases in which the lesions were limited to a bronchitis and peribronchitis.
2. Cases in which there were also larger patches of lobular pneumonia, discrete or confluent.
3. Cases showing widespread consolidation, often with hemorrhagic œdema, such as were commonly seen during the recent influenza epidemic.
4. True lobar pneumonia. Only one such case is included in the series.

But even this crude classification falls down, because it is very common for lesions of several types to occur in the same lungs. Indeed, the more cases that one studies, the more one becomes convinced that it is impossible to trace the effects of the initial chemical injury amidst the devastation wrought by the secondary bacterial invaders.

Perhaps the most characteristic and constantly recurring feature in the picture is the dark red zone of hemorrhage and partial atelectasis surrounding the small bronchi. This is most striking in the vicinity of the bronchioles. In a microscopic field we find the bronchus lined with a fibrino-purulent membrane or completely filled with exudate, the wall necrotic and infiltrated with wandering cells, the adjacent alveoli collapsed, filled with red blood cells, and outside of this, a zone in which the alveoli are filled with dense fibrin plugs. Bacteria, as a rule, are abundant only within the bronchus.

The partial or complete occlusion of the bronchi and bronchioli with exudate is no doubt responsible for the emphysema or areas of atelectasis so frequently present. It was very common also to find beaded rows of vesicles of interstitial emphysema, especially near the anterior borders: and in a few cases, there was extensive subcutaneous emphysema at the root of the neck and the upper part of the thorax.

Œdema, sometimes patchy, rarely intense and diffuse, was present in about two thirds of the cases. No attempt was made to estimate the amount by quantitative means. The lung-heart ratio, which is of considerable value in experimental work, especially with the suffocant gases, is of little use in the study of human material because of the complicating infectious pneumonias. From our autopsy records, which naturally vary greatly in detail and accuracy, it appears that an excessive œdema was noted only in three cases, dying respectively two and three days after gassing; a moderate general œdema was present in 23 cases, and a slight patchy œdema in 32 cases. In 16 cases the absence of œdema is specifically recorded, and in 4 cases no record was made.

Is the œdema the result of the direct action of the chemical irritant, or is it due to the secondary infection? The evidence is not sufficient to answer the question decisively. Even in the earliest cases in our series, an intense bacterial infection had supervened, and microscopically at least, early pneumonic changes were present in some parts of the lung. On the other hand, it is possible in rabbits (Pappenheimer and Vance) to produce a moderate pulmonary œdema by intravenous injection; and Lynch, Smith and Marshall have made similar observations in dogs.

The special complications in the lungs are those which occur with probably equal frequency in the primary bacterial pneumonias. Abscesses, areas of necrosis, gangrene, sero-fibrinous or suppurative pleuritis, organization of the pneumonic exudate—all these may be regarded as dependent upon the bacterial infection rather than the primary action of the mustard gas. There are, of course, many interesting histological details which will have to await fuller report of our material.

(c) *Lesions in Other Organs.*—The study of human cases affords very little evidence that mustard gas, through cutaneous application or by inhalation, may be absorbed and produce systemic effects in other organs. In dogs exposed to high concentrations in the chamber, the hydrolysis product—dihydroxyethylsulphide—has been detected in the urine, but so far as I am aware, no similar demonstration has been made in man. Clinically the group of cases with diffuse general pigmentation, marked apathy and asthenia, low blood pressure, and often pronounced mental symptoms certainly suggests a systemic intoxication which cannot be explained solely by the local action upon the skin and respiratory tract.

More direct proof of the absorption of ethyldichlorsulphide are the changes in the bone marrow and circulating blood. Zunz,[10] and later Krumbhaar,[11] have shown that severely gassed cases, after an initial leucocytosis, may develop a marked leucopenia, and similar observations have been made by Muratet and Fauret Fremiet[12] in animals. Experiments carried on in collaboration with Capt. Morgan B. Vance[13] have shown that intravenous injections of small doses in rabbits bring about a profound leucopenia, with destruction of the granulocytes in the bone marrow. The action in this respect resembles benzol.

(i) *Alimentary Tract.*—Abdominal tenderness, nausea, vomiting and less frequently diarrhœa are observed clinically in a large proportion of mustard gas cases. The experiments of Warthin and Weller, Lynch, Smith and Marshall, Pappenheimer and Vance, and others have shown that the intravenous or subcutaneous injection of mustard gas in animals may be followed by a hemorrhagic enteritis. Norris[14] refers the submucous hemorrhages of the stomach and duodenum to the swallowing of contaminated saliva, but the possibility of the elimination of the absorbed substance or its hydrolysis products through the alimentary tract, has not been disproved. The possibility is suggested by the experimental work above cited, and on clinical grounds by Ramond, Petit and Carrié.[15]

In our records, the alimentary tract was not examined in about half the cases; in about 25 per cent. the stomach and intestines are specifically stated to be normal; in the remainder, there are noted injection or hyperemia, sometimes of the stomach, more commonly of the small intestine; hemorrhages in stomach, small or large intestines, erosions or small ulcers—in three cases in the stomach, once in the small intestine, once in the colon.

Too much weight cannot be placed on these fragmentary references. The injection may be attributable to the general visceral stasis, which is the rule in the fatal cases. Hemorrhagic erosions of the stomach are so frequent a finding in any large series of autopsies, that their occasional presence in these cases does not seem very significant. On the other hand, a more careful scrutiny might have shown a higher incidence of gastro-intestinal lesions.

(*ii*) *Liver.*—We have found no significant changes, apart from those common to all acute infections. Cases dying early have not shown degenerative changes which might be ascribed to a specific effect of the mustard gas.

(*iii*) *Circulatory System.*—There are no definite alterations of the myocardium which might throw light on the later circulatory disturbances (effort syndrome) noted in a certain proportion of gassed individuals. Neither have we found any typical or characteristic vascular lesions in the lungs or elsewhere, which could not be of infective origin.

(*iv*) *Kidneys.*—The kidneys regularly show an intense capillary venous congestion. In one case only were there hemorrhages into the capsular spaces and tubules. No changes which would indicate a toxic effect upon the renal epithelium were noted. The intense congestion is probably sufficient to explain the diminution of urinary output, albuminuria, presence of casts and red blood cells, described by Hermann as typical urinary findings during life.

(*v*) *Central Nervous System.*—We have unfortunately no data upon possible finer alterations in the central nervous system. In very few cases was the brain examined, and we have no histological material. No facts of value have been deduced from the incomplete study of the adrenal gland and other organs of internal secretion which have been occasionally included in our material.

This preliminary survey of the human cases discloses the fact that we are still unable to answer the most important practical problem involved, namely, what permanent anatomical changes are produced in the lungs or elsewhere by the gassing, and what permanent functional disability may we expect as a result. It seems very probable that the widespread organizing bronchiolitis and peri-bronchiolitis will in many cases lead to stenosis and bronchiectasis, and that the metaplasia of tracheal and bronchial epithelium into non-ciliated cells of the squamous type, may be of importance in predisposing to subsequent respiratory infections. These, it seems to us, are the possibilities which should be kept in mind in further clinical and pathological studies upon the late cases.

3. *Poisoning by Gases of the Phosgene Type.*—A study of the few cases attributable to gases of the suffocant type which we have had the opportunity to examine, has added nothing to the now familiar picture. A brief description of a typical case will serve as an example:

There is a dusky, livid hue to the lips, ears, finger tips and dependent portions of the body. Thin blood stained fluid flows from the nostrils and mouth, or a "mushroom of foam" projects from the lips. Trachea and bronchi are filled with frothy fluid. Their mucosa is dark red, velvety and smooth, and there is no necrosis, ulceration or membrane formation. The lungs are bulky, meeting in the median line, completely filling the pleural cavities, showing often the imprint of the ribs. They are heavy and smooth, distended almost to their maximum capacity. The pleural cavities frequently contain a few hundred c.c. of blood tinged fluid. The color of the lungs is usually strikingly variegated—pale pink areas of emphysema alternating with dark red firmer patches, or even lobes of atelectasis and hemorrhagic œdema. The interlobular septa are wide and translucent from œdema. When the lungs are cut thin, bloody fluid pours out in quantity.

The heart, especially the right auricle, is distended, the blood dark and thick but the coagulability apparently not changed.

The remaining organs, apart from intense congestion, show nothing abnormal.

Microscopically, in the early cases, the œdema is visible either as a uniform pink staining material, or as a granular or shreddy coagulum. There is little or no fibrin. The capillaries are congested and tortuous; there is diapedesis of red blood cells, and in some areas more extensive alveolar hemorrhage and exfoliation of alveolar epithelium. The capillaries contain an abnormal number of leucocytes, a few of which emigrate into the alveoli and septal tissue. Their nuclei are karyorrhexic. The epithelium of the small bronchi may be lifted up from the membrana propria by the underlying œdema, and partly exfoliated.

The peribronchial and perivascular and subpleural lymphatics are distended.

The superficial epithelium lining trachea and larger bronchi shows a pycnosis of the nuclei, and a homogenization of the cytoplasm. Whether this is due to the phosgene alone or to the admixture of other more irritant gases, I am not able to state.

In one of our cases dying within twenty-four hours, there had occurred already a tremendous growth of Gram-positive cocci (probably streptococci) throughout the lung tissue, although there was only a beginning pneumonia. In the remaining early cases, the bacteria were practically limited to the bronchi.

Our material is not sufficiently extensive to enable us to make definite statements as to final and permanent alterations in the respiratory organs. The experimental work of Winternitz on dogs would indicate that such changes must be of frequent occurrence.

I wish in conclusion to emphasize again the importance of studying material from gassed individuals who have died of some incidental cause, preferably not a respiratory infection. It is only in this way that we shall be able correctly to appraise the final effects of the war gases upon the respiratory organs, and to form a correct idea of the amount of chronic invalidism for which they are responsible.

References

1. Lillie, Clowes and Chambers: Experiments on the Action of Mustard Gas on the Cells of Animal Organisms. *Science*, 1919, xlix, 382.
2. Marshall, Lynch and Smith: Dichlorethyl Sulphide (Mustard Gas) I. Systemic Effects and Mechanism of Action. *Jour. Pharmacol. and Exper. Therap.*, 1919, xii, 265.
3. Mackenzie, G. M.: Plates Illustrating the Pathological Effects Produced by Some of the Better-known Gases Used by the Germans. *U. S. Nav. Med. Bull.*, Washington, 1918, xii, 173.
4. Winternitz, M. J.: Anatomical Changes in the Respiratory Tract initiated by Irritant Gases. *Med. Surgeon*, 1919, xliv, 476. Also War Gas Investigations—Bureau of Mines, American University Monographs.
5. Warthin and Weller: Researches on Mustard Gas. Contributions from the Pathological Laboratory, Univ. of Michigan, 1918–1919, ix.
6. Great Britain Medical Research Committee: Reports of the Chemical Warfare Medical Committee. No. 9. Tissue Changes in Animals produced by Pulmonary Irritant Gases. London, 1918, 45, pp. 8.
7. Mayer, Fauret-Fremiet: Confidential Reports of the French Chemical Warfare Service.
8. Unpublished Report: Chemical Warfare Service, American Expeditionary Force.
9. Satier and Gaos: Deux cas d'insufficience surrénals aigue chez des soldats intoxiques par les gaz. *Jour. de med. et de chir. prat.*, 1918, lxxxix, 489.
10. Zunz: Report on Interallied Gas Conference, October, 1918.
11. Krumbhaar: Rôle of the Blood and Bone Marrow in Certain Forms of Gas Poisoning.
12. Muratet and Fauret-Fremiet: Personal communication.
13. Pappenheimer and Vance: Report to Chemical Warfare Service, American Expeditionary Force. Also *Proc. Soc. Exp. Biol. and Med.*, 1919, March 19.
14. Norris, G. W.: Toxic Gases in Modern Warfare, with Special Reference to Diagnosis and Treatment. *Jour. Am. Med. Assn.*, 1918, lxxi, 1822.
15. Ramond, Petit and Carrié: Les gastrites aigues conséculifs aux intoxications par le gaz. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1917, 3ieme, S. xli, 1167.

Discussion:

Dr. Baehr: The extent of my own experience with cases of gas poisoning on the post-mortem table is in no way comparable to that of Dr. Pappenheimer, and I therefore hesitate to speak in a discussion of his paper. But I have seen two examples of a condition which he has not mentioned, and one which is especially interesting from the standpoint of the diagnosis of tuberculosis. It is a lesion which affects not the trachea and larger bronchi, but solely the very small bronchi and bronchioles with destruction of the bronchial mucous membrane and an inflammatory infiltration about the smaller bronchi, of yellowish white appearance. Microscopically, this peribronchial infiltration was of chronic inflammatory character. The interesting thing clinically about these cases was that *x*-ray examination showed a condition which was absolutely typical of a general miliary tuberculosis. The entire lung was shot full of these small miliary foci, and on the post-mortem table the gross appearance at first glance was not unlike that of miliary tuberculosis. However, there was no difficulty in recognizing what the condition was upon more careful examination and microscopical study.

Dr. Mackenzie: I had an opportunity to see a good many dogs gassed in Washington. In many respects the lesions were quite similar to those just described, but I would like to ask Dr. Pappenheimer about one or two things. One thing which was very interesting, especially in the light of the pigmentation in human cases, was the frequency of hemorrhage in the adrenal cortex in dogs. Somewhere between 50 and 75 per cent. of the dogs showed hemorrhages in the adrenal cortex after inhalation of mustard gas. Have you observed anything of that sort in the autopsy material you have seen, Dr. Pappenheimer?

Dr. Pappenheimer: No, the lesions in the adrenals were insignificant. We did find focal necrosis occasionally, but this would be explainable by the concomitant infection. However, the preservation of many of the adrenals was such that we could not draw any conclusions, especially as to the chromaffin staining of the material. But I am sure that hemorrhages would have been recognized in the gross at autopsy, and I do not recall a single case of gross hemorrhage in the adrenals. In regard to Dr. Baehr's cases, were they following mustard gas or phosgene?

Dr. Baehr: The causative agent was supposed to be mustard gas, but this was only ascertained from the patient's statement, so that the etiologic agent could very well have been phosgene.

Dr. Pappenheimer: I have in some of my preparations found an obliterating bronchiolitis almost like an obliterating endarteritis, with great proliferation of the subepithelial tissue and narrowing of the lumen of the smallest bronchioles. It is curious that an organizing bronchiolitis was not often seen in these cases. The lumen becomes constricted from without rather than from the organization of the exudate within the lumen.

Dr. Mackenzie: Do you think from your observations that mustard gas produces a systemic change?

Dr. Pappenheimer: I do not think that we have any real right to have any opinion about that. The gastro-intestinal lesions which I should have mentioned are present in about one-third of the cases. Hemorrhagic erosions or sometimes real ulcers of the stomach, duodenum or small intestines may occur. Only a few cases showed lesions in the large intestines. I think the intestinal lesions have been variously explained by the swallowing of contaminated saliva, nervous reflexes, and so forth; there is no proof that they are due to elimination of the toxic gas or its decomposition products. On the other hand, the effect on the bone marrow and the leucopenia affords pretty good evidence of a systemic effect. It might be argued that many of these cases developed an intercurrent influenza and that the leucopenia was associated with that. However, a leucopenia was found by Krumbhaar in cases dying at a time when influenza was not prevalent.

I do not know whether I made my point clear in mentioning the resemblance to influenza. What I wished to bring out is, that it is often impossible to tell whether the pulmonary lesions which we observe are the direct effects of the chemical irritation or the effects of a secondary influenzal infection. The fact that we found lesions of this type when influenza was not about, and that similar lesions may be produced in animals by experimental gassing make one feel that the changes are due to chemical irritation. Dr. Winternitz has also been very much impressed with its resemblance.

Dr. Moschcowitz: In the experimental lesions in animals, have the bacteria been found also?

Dr. Pappenheimer: I do not know about influenza bacilli. Bacterial infection in general takes place very rapidly in animals after gassing.

Dr. Kline: There were forty-five mustard gas cases autopsied at Base Hospital No. 18. The pulmonary consolidation in practically all of these cases was peribronchial or peribronchiolar. None of the uncomplicated cases showed coalescing lobular consolidation, which is characteristic of a majority of influenzal pneumonias. I would like to know if you have seen coalescing lobular consolidation in any of the uncomplicated mustard gas cases.

Dr. Pappenheimer: Yes; we observed practically every type of pneumonia except a straight out and out lobar pneumonia. We did not have any of those in the series.

Dr. Kline: I wonder if the distribution of the consolidation was widespread throughout, or coalescing in type.

Dr. Pappenheimer: We had cases in which it was limited to the bronchi, but we also had cases in which it was very extensive.

A CASE OF CARCINO-SARCOMA OF THE BREAST

A. O. WILENSKY, M.D.

(*From the Pathological Laboratory, Mount Sinai Hospital, New York*)

The patient from whom this specimen was removed is a married woman of 48 years who for two years has presented the manifestations of an ordinary diabetes. In April, 1919, she came to the hospital to the surgical service of Dr. Elsberg with the story that for three months a lump had been noted in her left breast which was painless, and which had apparently grown little, if at all, until three weeks before she came to the hospital. Then the skin overlying the tumor became very dark one day, without any known preceding trauma, and, during the course of the next few days, it became lighter. The day before admission to the hospital, the tumor had suddenly increased markedly in size and the skin had again become very dark blue in color.

The physical examination demonstrated the presence of some enlargement of the thyroid isthmus and a moderate grade of exophthalmos. In the left breast was a globular mass the size of an orange, apparently attached to the skin and to the chest wall. The skin of the breast was diffusely ecchymotic and the cutaneous veins were dilated. The pre-operative diagnosis was a probably malignant tumor with hemorrhage.

Some acidosis was present and after this was controlled the patient was operated upon according to Halsted's method. This was followed by an uneventful convalescence and later the patient left the hospital apparently well.

Pathological Examination of the Specimen.—The specimen consists of the breast, the pectoral muscles and the axillary contents. The breast has a long incision disclosing a large cavity which, in the recent state, contained bloody serum. In the depths of the cavity are some shaggy remains of what is apparently papillary tumor tissue. The greater mass of tumor has been removed. The axillary glands are small and fatty and show no evidence of tumor involvement grossly.

Microscopically the stroma of the tumor is uniformly similar and consists of tissue which is sarcomatous. The cells vary as to type; there are small and large, round and spindle-shaped cells; and of these the round cells seem to predominate; there are large numbers of giant cells of either a round or irregular shape and

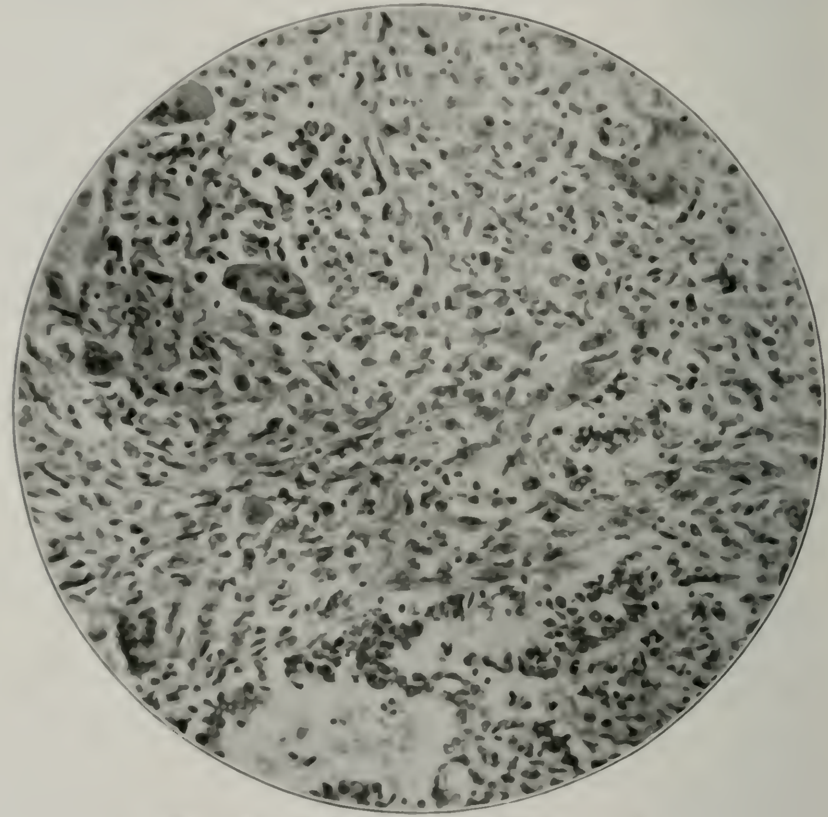


Fig. 1. Carcino-sarcoma of the Breast. (X 320.)

containing many nuclei. In the stroma are numerous islands of epithelial cells appearing either as solid cords or assuming gland-like topographies; in the latter a basement membrane can be distinguished in many of the gland-like structures, while in others the membrane is frankly broken and almost completely disintegrated. There is no regularity of distribution of the epithelial elements. In both the sarcomatous and carcinomatous elements there are many pyknotic nuclei and many mitotic figures. The tumor is not inflamed. (Fig. I.)

The tumor is evidently a malignant one and belongs in the broad group of mixed tumors. Altogether these tumors are very uncommon. Cases have been described in the generative organs, the kidneys, the œsophagus and other organs as well as in the breast. Upwards of twenty cases have been reported as having occurred in the breast; these include those reported by Barton, Benmosch, Herxheimer and others. It is more common to find tumors of different origin and structure growing in opposite breasts of the same patient.

When the composite tumor occurs in one breast the growth may consist of two separate nodules growing side by side, or the growth is a homogeneous one and the presence of tumor tissue of both meso- and epi-blastic origin is detected only by the microscope. In the latter cases some of the reports indicate that it was possible to recognize the dual nature of the tumor from the gross appearances of the cut section because of the presence of islands of differently appearing tissue. The concurrence may possibly result from two distinct tumors coalescing and blending and in some of the cases this assumption seems to be borne out by the fact that parts of the tumor were totally sarcomatous, while other parts were similarly carcinomatous. In others the microscopical picture is fairly uniform and the two elements seem thoroughly blended, even though in isolated portions one may seem to overshadow the other more or less completely; in these it seems that a single tumor with a dualistic structure has grown from the very beginning.

The relative proportions of carcinoma and sarcoma in any individual tumor may far exceed the other so that in some it seems evident that the tumor is a sarcoma in which the islands of carcinoma are definitely subsidiary; in others the sequence of events seems reversed and one obtains the impression that a sarcomatous transformation has occurred in the stroma of a carcinoma. The most common combination seems to be the first—a carcino-sarcoma. In the case which is being reported the pre-operative assumption was that we were dealing with a sarcoma; in most of the reported cases the supposition has been that the tumor was a carcinoma until the microscopical picture was identified.

Other changes have been reported in some of the tumors. Areas containing many giant cells are frequently found. In Coenen's case there were areas of myxomatous structure. Secousse's case was identified as a cysto-sarcoma with areas of carcinoma. Wehner's case was a spindle cell sarcoma; the carcinomatous portion was partly of the squamous cell type and partly it assumed an adenomatous structure and resembled a scirrhous carcinoma. A very extraordinary case was reported by Orth: a myxo-chondro-cysto-sarcoma was removed from a patient's breast; a local recurrence occurred which was a sarcoma containing nests of scirrhous carcinoma; the metastases were mostly carcinoma.

Lymph-gland metastasis has only occurred in some of the cases: only the carcinomatous element appeared. In the others an endothelial hyperplasia was present; in some the latter appeared in conjunction with secondary carcinomatous deposits. On the other hand metastatic formation which subsequently appeared in other parts of the body has most frequently been sarcoma. In Schlagenhaufer's case the primary tumor could be fairly well differentiated into a sarcomatous and a carcinomatous part; in the metastatic growths both elements were fused and sarcoma and carcinoma occurred in combination.

Tumors of this kind are more common in the ordinary laboratory animals such as mice and rats; in the latter animals it is supposed that a sarcomatous change takes place in the stroma of a carcinoma. This explanation has been applied to the human cases. On the other hand Krompecher believes these tumors to be entirely carcinomatous and that the areas which appear sarcomatous are in reality composed of cells which are epithelial in origin but which have assumed the morphology of the spindle cell.

Discussion:

Dr. Ewing: I do not wish to raise any suspicion about the occurrence of mixed carcino-sarcoma of the breast, but I am inclined to agree with Krompecher that the capacity of epithelial cells in malignant tumors to transform themselves into spindle and giant cells is very generally underestimated. I do not think that it is at all impossible for both these tumors to have been originally pure epithelial growths. In Dr. Wilensky's case there are giant cells almost identical with many of those seen in Dr. Jessup's case. They look like foreign-body giant cells. In Dr. Wilensky's case there are very irregular, but clearly defined, epithelial structures which are missing in Dr. Jessup's case. Both tumors are sharply circumscribed, which is strongly in favor of an epithelial origin. Yet how can one draw conclusions as to the origin of a growth when one has only seen a few sections of a very advanced stage? It is pretty clear that we are here seeing a secondary structure. I think it would be very interesting in this case to refer to the Committee on Microscopy the gross material and the microscopical sections.

Dr. Wilensky: About five months ago Dr. Geist and I looked up all the cases of sarcoma of the breast which we had in the laboratory and found about twenty of them. None of the twenty appeared like either of the two tumors shown here to-night. I think there must be the records of at least one thousand breast tumors in the laboratory by this time and the specimen to-night is different from all of them. It is difficult to say from the end results of these tumors just what happened originally, especially in this case. I am inclined to think that both elements began growing at the same time. It seems to me that in most of the sections both the carcinomatous and sarcomatous elements are very well mixed. The picture in one section seems to be essentially sarcoma with a great many giant cells; these I think are foreign-body cells.

A CASE OF GIANT CELL SARCOMA OF THE BREAST

D. S. D. JESSUP, M.D.

This tumor of the breast seemed worth while presenting, as it is a rather unusual type, and I have been unable to find any similar descriptions in the literature. It is a sarcoma of the breast characterized by a very large number of giant cells. The history of the case is that of a woman of thirty-five on the service of Dr. G. H. Semken at the New York Skin and Cancer Hospital. She had a tumor in the breast for six months with some pain and with a slight discharge from the nipple. Examination before operation showed a very hard nodular, sharply defined tumor in the upper part of the breast, not far from the nipple. No axillary nodes were found. The breast was removed with the tumor and examination showed a sharply circumscribed mass about the size of a hen's egg and very hard on section, with some small areas of hemorrhage scattered through it. It was very different from the appearance of the usual scirrhous carcinoma. In the axilla there were a number of enlarged nodes which seemed broken down.

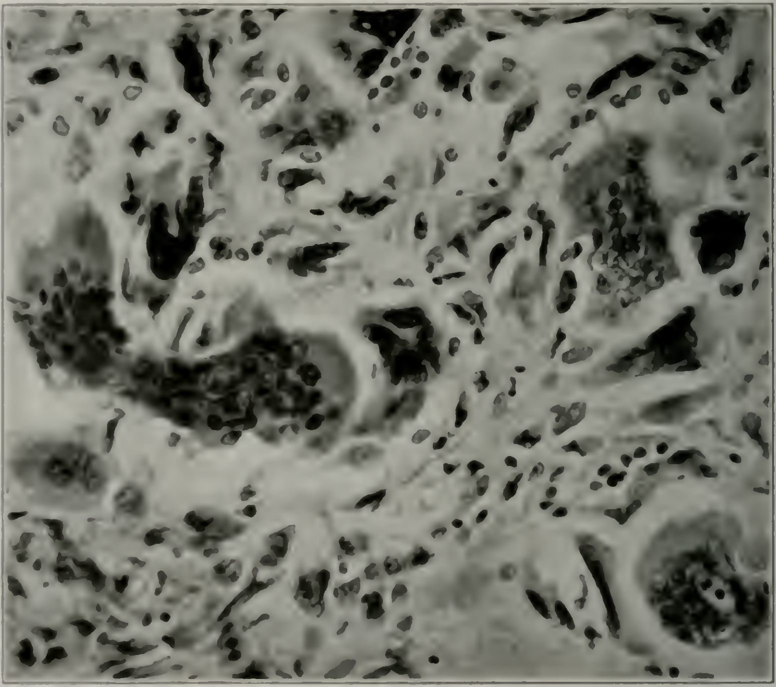


FIG. 1. Giant cell sarcoma of breast. High power, × 300. Some of the giant cells show large numbers of nuclei.

Microscopical examination showed a spindle cell sarcoma, in the more cellular portions of which were large numbers of giant cells varying in size, some being two or three times the size of the surrounding cells, and others containing sixteen or more nuclei. (Fig. 1.) The giant cells appeared to be of the foreign-body type The stroma itself was very dense. Some of the large blood vessels showed obliterating endarteritis. (Fig. 2.) Three or four of the axillary nodes were invaded by the same type of sarcoma with giant cells.

The noteworthy feature seemed to be that we have here a sarcoma with giant cells, a type of tumor which ordinarily does not appear in the breast, and that this giant cell sarcoma is evidently a malignant type of growth, with lymph node invasion, differing from the giant cell sarcomata which we find in the bones, for instance, which are relatively benign.

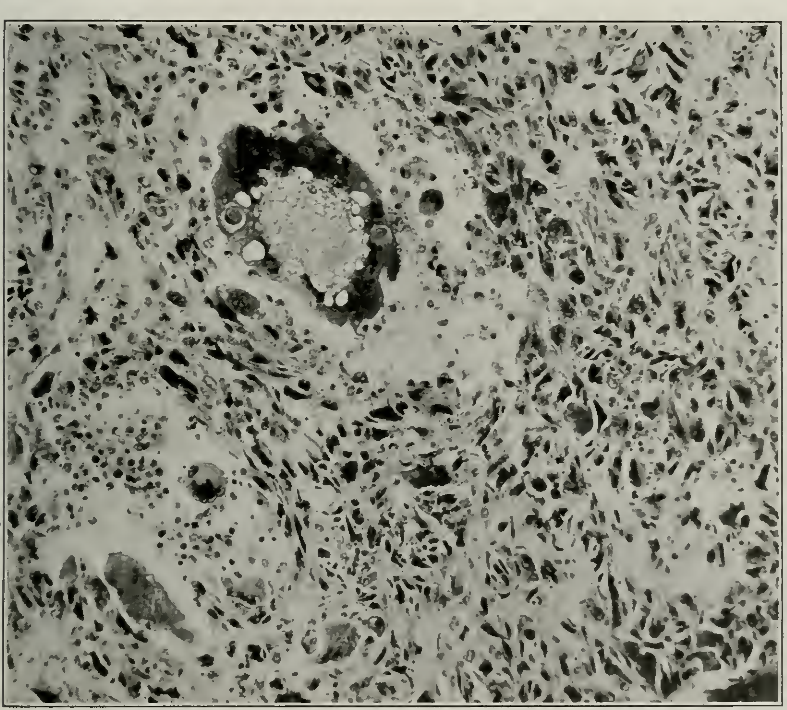


FIG. 2. Giant cell sarcoma of breast. This same type of new growth also found in the axillary nodes. The large giant cell contains fat.

Discussion:

DR. EWING: I would like to suggest that this case be referred to the Committee on Microscopy for a report. It is evidently a very rare and interesting tumor, and I think that it deserves the attention of the Microscopy Committee.

DR. MOSCHCOWITZ: Were the bones of the body excluded as the primary source?

Dr. Jessup: Dr. Wood suggested *x*-raying the patient, and we will arrange to have this done. On physical examination no tumors were noticeable in the bones.

Report of the Committee on Microscopy:

Dr. Ewing: The sections of the breast tumor show a cellular neoplastic growth composed of many large giant cells resembling those of the epulis giant cell sarcoma, associated with many smaller polyhedral and spindle cells, some lymphocytes, and slight vascularity. The giant cells are not exactly like those of the epulis, the nuclei being fewer, many nuclei being large and multilobed, and mitotic nuclei being numerous. The smaller cells infiltrate the fat tissue actively like carcinoma. The tumor is clearly malignant. In the axillary node the giant cells are scanty, while the others are smaller and more polyhedral.

The origin of this growth seems quite obscure. I cannot regard it as a simple osteogenic giant cell sarcoma, since this tumor is benign and does not produce lymphatic metastases. There is no indication that the growth involved bone. There is no trace of breast tissue in the section, so that the relation to the breast is doubtful. The possibility of a teratoid origin might be considered.

The gross anatomy of the tumor is that of mammary cancer, and I am disposed to regard it as such, attributing the unusual structure to some factors in the origin and course which do not appear in the history.

Dr. Norris: I do not believe that the tumor was primary in the breast. There is a considerable amount of shrinking due to the paraffin preparations of the sections. In my opinion, the tumor is primary in the bone—where, of course, I do not know. The connective tissue is distinctly osteogenic in type. *X*-ray examination will probably clear up the case. It is somewhat hazardous to express an opinion upon the malignancy of the growth, and I do not venture to state whether the tumor corresponds to the type of multiple tumors, which are comparatively benign, described by Martland before the Society, or whether it is a giant cell sarcoma springing from the periosteum. The point made that the axillary lymph nodes are involved is of comparatively little significance in a differential diagnosis.

Dr. Wood: As I at first told Dr. Jessup, I believed the tumor is a primary bone tumor of the giant cell type, originating somewhere in the bony skeleton. There has been a great deal of loose talk among the surgeons about these bone-marrow tumors all being benign, an opinion which is, I think, quite incorrect, for while some of the bone tumors are unquestionably benign, others, my experience leads me to believe, are malignant. The morphology does not always offer a certain guide to the ultimate course of the disease.

A PATHOLOGICAL CLASSIFICATION OF NEPHRITIS BASED UPON CLINICAL FINDINGS

I. J. LEVY, M.D.

(*From the Strecker Memorial Laboratory of the New York City Hospital*)

Since the introduction of the more practical methods in the study and diagnosis of the metabolism in nephritis, the necessity of a "workable" pathological classification for a clearer conception of the subject is apparent. Clinical classifications and those based on certain metabolic changes are now in popular use. They answer fairly well as a guide for therapeusis, but give very little information about the pathology, which after all is the important factor in the prognosis of disease. Our problem then was to adopt a classification which would "fit" the clinical entities commonly seen in those suffering with nephritis and at the same time include the disturbances in the nitrogen, salt, and water metabolism, and dye excretion which may be present in these individuals. In this we have partly succeeded, that is, we have seen that the common clinical nephritic pictures present disturbances in metabolism varying mostly in degree, but usually associated with, if not dependent upon, a definite pathological process in the kidney.

This is a preliminary report based on the study of a number of cases during the past three years by Dr. John Larkin and myself. I want to emphasize that any attempt anyone may make at a new pathological classification of nephritis can present nothing new. Practically every pathological change has been described by one pathologist or another. The clinician, unfortunately, has disregarded many of the types and has failed to build any structure upon which he might correlate the clinical entities and the pathological processes.

It is now generally conceded that the inflammatory or degenerative changes seen in kidney pathology have their origin in one of the three important radicles of the kidney, *i.e.*, the glomerulus, the tubules, or the vessels. Glomerulo-nephritis, through the description of various authors, is fairly well understood and the clinical manifestations of this disease, dependent upon this pathological type, are being more clearly appreciated.

Tubular nephritis, or the so-called nephrotic kidney, belongs to the group of kidney pathology which is associated with very definite clinical manifestations. You note that I state "is associated," for I think it has been fairly conclusively shown that the symptoms in this type are not dependent upon the kidney lesion, but are due to some metabolic disturbance outside the kidney.

We now come to the consideration of the term "interstitial nephritis." Both from a pathological as well as a clinical point of view it is unfortunate that this term has come into popular use. It is undoubtedly the cause of much of the confusion experienced by men in the diagnosis of chronic nephritis. Interstitial changes in the kidney are the result of either an inflammatory or degenerative process in the kidney parenchyma. Independent of the origin of the inflammation or the degeneration the response in the kidney parenchyma is the same—either a round cell infiltration and connective tissue replacement, or both. The process differs only in its location, degree, and extent; and *primarily in its course*. It is these factors which give us differentiation in the pathology with the resultant clinical pictures which are either dependent upon, or associated with, the kidney pathology.

Interstitial nephritis, as the term is understood, is generally an arteriosclerotic kidney. Usually accompanying the interstitial changes in the kidney are various grades of sclerosis of the vessels. In glomerulo-nephritis this is distinctly a secondary process. Simultaneously with the productive inflammation in the glomerulus early sclerotic changes can be noted in the vessels. Later, when the tubular elements have undergone degeneration following hyalinization of the glomeruli, the arteriosclerotic changes are already quite marked. And when the process has involved the organ to such an extent that its structure is not recognizable (complete hyalinization of the glomeruli and connective tissue replacement of the destroyed tubules) the vascular elements present the extreme stages of atherosclerosis involving the smallest vascular radicles of the kidney, *i.e.*, the vasa afferens and the vasa efferens. This is a typical pathological picture of an interstitial nephritis which had its origin in an inflammation of the glomeruli and following a definite pathological course has reached an "end stage" in which all the secretory elements of the kidney are destroyed. Such a process may take only months, or as many as fifteen or twenty years.

In individuals suffering with general arteriosclerosis, interstitial changes are seen in the kidney similar to those present in the other organs. They are secondary to the vascular lesion. The larger vessels of the kidney at first are involved, affecting various portions of the parenchyma. Depending upon the severity of the sclerosis of the particular vessel supplying the part, individual areas may present various stages of hyalinization of the glomeruli, with round cell deposits and connective tissue replacement of the affected tubules. You note this is definitely a focal process differing in this respect from the diffuse involvement seen in the glomerular type. Probably because of the nature of the lesion the course of the disease covers a period of years and seldom does it ever reach a stage seen so commonly in the glomerular type in which the organ appears structureless. Usually the kidney structure is well preserved, though the contraction of the organ may be fairly extreme. Only occasionally and then in very old individuals who have suffered from arteriosclerosis early in life does the interstitial process ever reach the extreme or "end stage."

Primary disease of the vessels of the kidney, apart from general arteriosclerosis, is probably the most interesting phase of kidney pathology. Not until Jores in 1908 emphasized the fact that arterial changes in the kidney occurred independent of general arteriosclerosis did this interest to any great extent the pathologists. Since then this type of kidney has been described by a number of men, but it has failed to arouse much enthusiasm among the clinicians. The earliest evidence of trouble is seen in disease of the smallest vascular radicles, *i.e.*, the vasa efferentia and the vasa afferentia. Seen in the pure type (we speak of a pure type because there is reason to believe this is a forerunner of another pathological entity) the kidney parenchyma looks surprisingly normal. A few glomeruli may be hyalinized with small areas of round cell deposits and some connective tissue changes, but the striking feature is the marked arterial changes of the very small vessels, so marked that many undergo complete thrombosis. I do not intend to discuss the associated pathology, but will mention that the largest hearts noted in kidney disease are met with in this type.

In studying a series of cases of nephritis and following them to autopsy one must be impressed with the frequency with which one meets individuals about the age of forty or fifty who present unmistakable signs of Bright's disease with no previous history of kidney trouble, and in whom the kidney picture closely resembles the "end stage" seen in glomerulo-nephritis. The process however does not begin in the glomerulus. We agree with Vollhard and Fahr that it is primarily and essentially a disease of the small arterioles. It is further taught by them that superimposed upon these arterial changes there is a productive inflammation of the glomeruli of unknown etiology which is the forerunner of the parenchymatous changes. This we have been unable to substantiate. For the present we are prepared to state however that there is a pathological entity resembling the secondary contracted kidney (glomerulo-nephritis). It differs from it chiefly in the fact that it is associated or dependent upon *primary* disease of the arterioles. This type of kidney is found in individuals who during life present a definite clinical and metabolic entity differing materially from that seen in a chronic glomerulo-nephritis.

Finally interstitial inflammation occurs as a result of a previous degeneration of the epithelium of the convoluted tubules (nephrotic kidney). This is apparently an uncommon condition, except in individuals suffering with a long standing chronic infection. Unfortunately we have not had an opportunity of studying this entity clinically, but have reason to believe it should afford no difficulty in diagnosis.

Interstitial nephritis then is not a pathological entity. It is a comprehensive term including a number of organic processes in the kidney, each having its beginning in an independent radical of the kidney. True, the end process in each is indistinguishable from the others. Nevertheless it can be definitely shown that each follows a course suggestive of a pathological normality, whereby in most instances one can be separated from the other. Because of this fact we offer the following pathological classification which we believe coincides with the various clinical phenomena.

1. Glomerulo-nephritis.
2. Tubular nephritis (nephrosis)—interstitial nephrotic kidney.
3. Arterio-sclerotic kidney.
    - *A.* Secondary (following glomerulo-nephritis).
    - *B.* Primary
        - General arteriosclerotic kidney.
        - Genuine arteriosclerotic kidney.
            - Pure type.
            - Complex type.

Discussion:

Dr. Libman: I would like to speak about one point that Dr. Levy raised, and that is the relation of the marked enlargement of the heart described by Dr. Levy in the cases of the arteriosclerotic type. I would like to say that you do get a marked hypertrophy of the heart in these cases, but it bears no direct relation to the kidney lesion. When the hypertrophy occurs, it is often I believe due to disease of the arch of the aorta, with loss of elasticity, the main trunk of the aorta not helping the heart. The heart then has to hypertrophy if the circulation is to be adequately carried on.

Dr. Moschcowitz: In the November number of the *American Journal of Medical Sciences* I have placed on record my views on the pathology of nephritis associated with hypertension. At this time I shall give a brief résumé of these views. Dr. Levy's classification is simply another of a legion that have appeared in the past. I do not think that there is anything more confusing than to read text books on classifications of nephritis. There are no two classifications that are alike. Now there is a reason for this. I believe the mistake consists in the fact that pathologists have tried to regard the "types" of nephritis that are found at autopsy as end products. In my pathological experience it has appeared to me as though the various "types" of kidneys are rarely pure, but always mixed, and are really stages of one and the same pathogenesis and if one collects a sufficient number of such kidneys one can trace a series in which the following main types are manifest. In the first, there are a few changes in the glomeruli, round-celled infiltration in the cortex, and the slight parenchymatous change. The next type is the so-called "white" kidney; this is succeeded by the mixed white and red kidney, then the red kidney, and finally the contracted kidney. The only one of these kidneys that may be considered as an end result is the contracted kidney, and it is hardly conceivable how such a contracted kidney could have resulted without having passed through such stages as I have described. I believe therefore that the distinction between primary and secondary contracted kidney is hardly justifiable on morphological grounds. These kidneys may be regarded in a measure as having undergone a chronic granulomatous-like change comparable entirely to that which we see in the liver, urethra, ovary, etc., and in the conversion of granulation tissue into scar tissue. If you therefore find a certain type of kidney at autopsy it does not mean that the patient died as the result of that particular lesion. It simply means that the patient died in a certain stage of a pathogenesis and that if the patient had lived long enough the kidney would have shown a more progressive stage. These patients do not die so much as a result of a nephritis as from decompensation consequent to the hypertension. I believe this conception will simplify our understanding of the pathology of nephritis greatly. I do not believe it is right to classify kidneys simply on the basis of the predominant lesion of the organ. The lesion in nephritis is always a diffuse one involving all the components—glomeruli, epithelium, connective tissue, and blood vessels. Why it affects one component more than the other I cannot say. These observations are paralleled by clinical findings. Patients with hypertension vary from those who have little or no disturbance with kidney function to those with the advanced evidences of Bright's disease. It is impossible, except within narrow limits, to predict the "type" of kidney we shall find from clinical data alone and I believe the conception I have outlined above furnishes the explanation.

Dr. Larkin: We have been trying to arrive at some definite conclusions as a result of studies made not only at the bedside, but also from a metabolic standpoint, and we have tried to follow these cases to the autopsy table. This is only a preliminary report, and we would not want to say that the deductions we have drawn to-night are final. Perhaps at a later meeting we will take a little more of your time and show further studies of these cases.

Dr. Levy: I am glad that Dr. Libman touched on the cause of the cardiac hypertrophy. We find these two things associated—these very large hearts and marked arterial changes in the small vessels. The patients have a definite hypertension. I am unable to say whether this hypertension is secondary to the changes going on in the small vessels of the kidney, or whether the hypertrophy and changes in the kidney are due to one and the same cause acting simultaneously, or as Dr. Libman suggests, are secondary to some change in the aorta. It is true as Dr. Moschcowitz points out that there has been great difficulty in diagnosing these types pathologically, and that some men are of the opinion that the changes in these various types are one and the same. It is only within the last few years with the assistance of the metabolism studies that we have been able to clear this point. The term interstitial nephritis is too elastic; it includes too much. An interstitial kidney associated with general arteriosclerosis never causes the patient's death. On the other hand when you find an interstitial kidney on the autopsy table that followed a glomerular process you may be fairly sure the individual died from his kidney lesion. Patients with tubular nephritis do not die from their kidney *per se*. They usually get well or die of a terminal infection.

CYSTICERCUS OF THE FOURTH VENTRICLE

LEO LOEWE, M.D.

I wish to present to-night the pathological specimen from a case of cysticercus of the fourth ventricle, which was diagnosed during life, the diagnosis being confirmed at post-mortem examination. The patient was a Bohemian, aged 36, a cooper by occupation, whose chief complaint on admission was headache and vomiting for eight months. His personal and past history were negative, except for indulgence in thirty glasses of beer a day. Lues was denied. His complaint of headache was of eight months' standing. His headaches began in the occipital region and radiated to the vertex where the most severe pain was experienced. These headaches were aggravated by any sudden movement of the head. He had annoying diplopia, his disturbances of vision eventually becoming so marked that he was unable to read. He had vertigo for the same period of time, which was so intense as to interfere with his walking. Associated with these he had almost daily attacks of vomiting, which could be brought on by sudden movements of his head. His only other complaint was progressive weakness and loss of 50 pounds weight in three months.

Physical examination on admission showed a well-developed man who was evidently emaciated. His head was held rigidly, the patient showing disinclination to move it in any direction. Movement upward was particularly distasteful, bringing on immediate headache, vertigo, and nausea. He had a nystagmus in all directions and in all positions. His pupillary reactions were negative. His fundi showed some increase in retinal striations and slight blurring of the disc margins, and some engorgement of the veins. Aside from these facts his neurological findings were practically negative. He had no nodules in the skin.

The Wassermann reaction was negative in the blood and spinal fluid. The urine was negative on several occasions, no sugar being found. The blood count showed normal hemoglobin and red and white blood cells; there was no eosinophilia. The stools were negative for ova and parasites. Lumbar puncture revealed a clear fluid under slightly increased pressure with a count of 35 lymphocytes per cmm. There were no eosinophiles.

During his eleven days' stay in the hospital the patient's condition was very variable. There were periods of severe headache, nausea, and vertigo, but for the greater part he was entirely free from symptoms. His condition gave no warning of the sudden death which was to follow, except that in the last twenty-four hours his headaches were more frequent, and were associated with poor cardiac action.

Dr. Baehr performed the autopsy. There was distinct flattening of both cerebral hemispheres with uniform dilatation of the lateral, third and fourth ventricles. On the floor of the fourth ventricle was a pedunculated cyst covered by ependyma which formed the pedicle of the cyst. On removing the ependyma a club-shaped mass was disclosed. This pedunculated cyst was evidently capable of swinging about, thereby occluding the foramen of Magendie. On the floor of the fourth ventricle there were areas of proliferated ependyma. Microscopical section through the fourth ventricle showed marked thickening and infiltration of the ependyma with round cells. There were capillary hemorrhages and the formation of large multinuclear foreign-body giant cells. There was some periarterial infiltration of lymphocytes. The cyst showed the typical appearance of the cyst which is reproduced by Waterhouse in the *Quarterly Journal of Medicine*, volume 6, 1912–1913.

Cysticerci have been known in the pig since olden days. Göze first showed the true nature of the condition in 1784. Two years later Werner found it in the human. That the cysticercus found in the human is usually that of *Tænia solium* was first shown by Küchenmeister in 1855. Danger of infection with *Tænia solium* is greater than with any other form.

In 5,300 autopsies in Berlin systicercus was found in 87 cases, 72 of these being in the brain. In the same number of autopsies in Prague cysticercus was found in 28 cases. In 1,400 autopsies in Munich it was found in 2 instances, both being in the brain.

The German literature of course abounds in cases of cysticercus. There is a scarcity of such literature in this country.

In humans, the brain is the seat of predilection for cysticercus; only in muscles and underneath the skin are the parasites encountered more often. Usually we are dealing with a single cysticercus. Heller, however, once found 60 in one brain, whereas Delore and Bonhomme described a brain with 111 parasites.

One may find cysticerci underneath the skin, under the tongue, and in the eye. In the brain they may be lodged in the brain substance, in the meninges, or they may be free in the ventricles and subarachnoid space.

The reaction of the surrounding brain substance in the neighborhood of the cysticercus varies greatly in intensity and character. Microscopically the findings may be negative. Occasionally one finds some disintegration of tissue, with coagulation necrosis, capillary hemorrhages, and formation of corpora amylacea. In Stamm's case of cysticercus of the fourth ventricle in the immediate vicinity of the cyst there was an accumulation of pigment, then a layer of multinuclear giant cells and in relation to this a well-defined region infiltrated with lymphocytes. Perivascular infiltration with round cells was also present. The ependyma of the fourth ventricle was greatly proliferated. The pathological report on Stamm's case could very well be substituted for a report of our own tissue sections.

References

1. R. WATERHOUSE: *Quart. Jour. Med.*, London, 1913, vi, no. 24.
2. KÜCHENMEISTER: Die in und andem Körper des lebenden Menschen unkommendem Parasiten. Leipzig, 1858.
3. HELLER: Invasimiskrankheiten. V. Zumssen's *Path. u. Therapie*, 2. Auflag, 3 lb., 1876.
4. DELORE AND BONHOMME: *Arch. gen. de Med.*, 1865.
5. STAMM: Ein Fall von Cystecercus im 4 Ventrils Bd., Inaug. Diss., Göttingen, 1892.
6. EVANS: *Bull. Johns Hopkins Hosp.*, 1915, xxvi, 87.

Discussion:

DR. MOSCHCOWITZ: I would like to mention that the diagnosis was made during life by Dr. Loewe himself.

DR. LOEWE: Clinically the diagnosis depends on the presence of cerebral phenomena which are very variable. That is, there are periods of intense headache, vertigo, and vomiting, with nausea, alternating with periods when there is entire freedom from these symptoms. The pain and stiffness of the neck, the vomiting and cerebellar ataxia are indicative of some tumor or pressure in the posterior fossa, whereas the choked disc which is slowly progressive, the slow pulse, somnolence, and the headaches are suggestive of intracranial pressure. Rarely there are some localizing symptoms which would help, as for instance, diabetes or respiratory phenomena or cranial palsies. The best confirmatory test is that described by Bruns, which consists in brusquely moving the head of the patient around, with the instantaneous production of headache, nausea, and vertigo. I may say that Bruns' test is present in only about one fourth of the cases. Then again the fact that these people die suddenly is very typical. The presence of vague cerebral symptoms in a person, who harbored nodules in the skin, under the tongue or in the eye would, of course, give rise to the assumption that the parasites were in the brain, and the presence of an eosinophilia in the spinal fluid would be definite evidence of the presence of cysticerci. The presence of eosinophiles in the circulating blood would suggest the diagnosis in an individual with unexplained cerebral symptoms. In a case of Evans' the diagnosis was made by finding the calcified body through the *x*-ray, but of course the diagnosis was suspected. In our case the diagnosis was based on firstly the patient's nationality and occupation. There was absence of sufficient grounds to warrant a diagnosis of lues or a cerebral tumor, or of hysteria, a diagnosis which has been made in the German cases. It was the variability of the man's symptoms during the time he was in the hospital that made one strongly suspect the diagnosis. I can thank Dr. Libman for mentioning it one day on the ward, and I recalled the peculiar behavior of these patients. The diagnosis was confirmed by the fact that on moving the head it brought on nausea, headache, vomiting, and vertigo, and the fact that this sign was so constant. A definite aid to the diagnosis lay in a history of having had a tapeworm.

Dr. Libman: There is not much that I can add, Dr. Loewe has covered the ground so fully. He said the diagnosis was based in this case on the presence of the Bruns' sign, that is, on the production of vertigo on sudden movements of the head, either by the patient himself, or by the observer. That symptom was described as far back as 1902. It is important to note, as Dr. Loewe said, that you do not get this in all cases. There was a case described by Barany in which he diagnosed a lesion as being located in the left half of the cerebellum, and post-mortem examination showed a cysticercus in the fourth ventricle. On the other hand, the presence of the symptom is not pathognomonic. You cannot make a diagnosis of cysticercus of the fourth ventricle unless you have contributory facts. Such observations were made by Rudolph Schmidt, who showed that sudden changes in the position of the head could bring on headache in conditions other than cysticercus of the fourth ventricle. Oppenheim described a case in which this sign was present, and there was located a serous meningitis at the base, in the posterior fossa. The symptom is of most value if the patient is one who has periods in which he has headache, vertigo and pain, especially in the back of the head, and then he has periods in which he is free from these symptoms, and if in the free periods, the Bruns' symptom is present. There is another symptom which is valuable, which has been pointed out by Oppenheim, and that is the mental changes. The mental symptoms are very curious. You may have hallucinatory conditions; you may have dementia, and neither need be constantly present. There occurs also a peculiar confusional state which enabled Oppenheim to diagnose two cases. Clinically this might be of some value in making the diagnosis. It is remarkable that you can open the fourth ventricle and look for lesions and still have the patient live. This was suggested by Bruns, and many years later the fourth ventricle was opened in a case of suspected cysticercus and nothing was found. At autopsy a localized serous meningitis was found. It is important to remember that Bruns' symptom can be present whether the cyst is a floating one or is attached by a pedicle.

PERIARTERITIS NODOSA

GEORGE BAEHR, M.D.

(*From the Pathological Laboratory of the Mount Sinai Hospital, New York*)

A few years ago Dr. Lamb demonstrated two cases of periarteritis nodosa before this Society, and at that time he took the opportunity of reviewing the literature so thoroughly that there is no need to do so to-night. This case is different from the two he presented in showing certain features which were not previously well described. In other words, this rare condition is in this instance made still more rare by having features which are not present in most of the reported cases, or if present, have been neglected in all descriptions of the microscopic picture.

Concerning the interesting clinical aspect of the case, I would like to ask Dr. Manges to tell you the details, as the man died on his service. The patient was admitted to the surgical service of Dr. Edwin Beer at the Mount Sinai Hospital in June of this year. Previous to that time he had suffered from attacks of pain in the legs, and he entered the hospital with an attack of acute abdominal pain. The patient was operated on, an exploratory laparotomy being done by Dr. Leo Buerger, and in the mesentery certain nodular swellings on the branches of the superior mesenteric artery were found. From these findings a diagnosis of periarteritis nodosa was made.

The excised material which was sent to the laboratory consisted of nodular swellings on the wall of a branch of the mesenteric artery, and under the microscope these showed the very early lesions of periarteritis nodosa. An acute inflammatory infiltration involved the adventitia and media, resulting in their destruction, with rupture of the membrana elastica interna and the formation of a false aneurysm. After the operation, the symptoms of the illness persisted, the patient exhibiting an irregular fever, constant pain along the course of various arteries, chiefly in the limbs, and occasional attacks of abdominal pain. Eventually, encouraged by a slight improvement, the man left the hospital only to return shortly before he died, with the clinical picture of renal insufficiency, *i.e.*, general anasarca and uremia. Death occurred from this cause on October 8, 1919.

On the autopsy table remarkable changes were found in the arteries of the entire systemic circulation. These changes consisted grossly of an irregular thickening of all the arteries with occasional nodular formations on their walls. Upon microscopical examination, much to our surprise, nowhere in the vascular system was there found any evidence of the early acute inflammatory lesions of the vessel walls which were seen in the material removed in June on the operating table. The microscopical picture was rather that of a healed lesion. Throughout the arterial system there was a patchy scarring in the media with degeneration of the membrana elastica interna, and in many of the arteries, consequent on that, an irregular compensatory thickening of the intima. In the damaged vessels that had failed to withstand the strain, rupture of the wall had taken place, usually with the formation of false aneurysms. Other vessels had dilated at various places and formed true aneurysms. Many of the aneurysms, both true and false, were thrombosed, and had undergone complete organization of the thrombus with recanalization.

The remarkable thing about the microscopical picture was that the case was apparently one in which the acute process had disappeared, and the condition was now really one of healing. The patient died because of a sequela of the disease, the sclerosis in the kidneys.

The kidneys were very much changed. The right had a large false aneurysm, the size of a goose egg, beneath the capsule. Both organs were about half their normal size, contained many small dense scars and in the cortex were numerous small aneurysms, some the size of a pea, while others were so small as to be just visible. All the arteries in both kidneys were thickened, and along their course these aneurysmal changes were present. As the result of this extensive disease in the arterial system of the kidneys there had apparently occurred an atrophy of the parenchyma with consequent fibrosis and contracture. Microscopically nothing was left in the cortices of either organ, except shrunken cords of tubular epithelium, consisting almost exclusively of nuclei, and apparently well-preserved glomeruli, buried in dense connective tissue.

Other organs showed the presence of aneurysms, as for example the hepatic artery at the hilus of the liver, the splenic at the hilus of the spleen, and along the course of the bronchial artery. No macroscopic changes were found in the cerebral arteries, but microscopically, changes could be demonstrated. The stomach showed a chain of aneurysms about the size of peas, chiefly along the lesser curvature, and more especially along the course of the coronary artery of the stomach. The mucous membrane of the stomach was intensely congested and hemorrhagic and showed on the posterior wall three or four shallow ulcers. The relationship of these ulcers to the aneurysms and to the disease in the blood vessels could not be satisfactorily demonstrated. The heart showed the same disease of the coronary vessels as was found in the systemic circulation throughout the body, that is, irregular thickening of the wall with the formation of aneurysms along the descending rami of both coronaries.

The case differs from those previously reported in that the vessels presented the healed lesions of periarteritis nodosa, the end results of the process, in contradistinction to the acute lesions which have been described in most of the reported cases.

Discussion.

Dr. Manges: I shall limit my discussion to the clinical side. Thirty-eight cases of this strange disease have been reported, and each one is quite exceptional in its clinical data. This case is even more exceptional than the others reported, that is, in its clinical features and in its tendency to healing. It seems hardly credible that an individual having such an arterial system should have lived as long as he did, and as comfortably as he did. If it had not been for the renal condition, I believe that the man might have had a chance to recover. Kussmaul reported the first case, and that was a case of recovery. The patient died one year later as the result of a portal thrombosis. To refer to the clinical side, this man was 38 years old. Six or seven days before admission the patient had had pain in the left calf, radiating into the foot. In the next week he had similar pain in the right calf; in the following week he developed pain in the left groin, which radiated into the testis. A week later he had a similar pain in the right side, going into the testis. An irregular temperature developed and the man became very sick. Six days before admission to the hospital the pain was located in the epigastrium, and was associated with fever. When he was admitted to the hospital the case was diagnosed as an acute surgical condition; it was considered that it might be an acute pancreatitis or a ruptured gastric or duodenal ulcer. He was admitted to the service of Dr. Edwin Beer, who was particularly interested in the case. I have Dr. Beer's notes here, which I will read you:

"This patient was admitted to my wards in the evening, apparently suffering from what appeared to both the admitting physician and house surgeon as a perforated gastric or duodenal ulcer. When the patient was seen shortly thereafter by my associate, Dr. L. Buerger, he thought that the patient had some condition in the upper urinary tract, and cystoscoped him, catheterizing his ureters.

"The next morning on my visit the patient was cheerful and felt perfectly well, in fact as he was being taken to the *x*-ray department he asked me whether he could not go home that day.

"The physical examination was practically negative, though the patient was running a temperature, and had a high leucocyte count (from 34 to 56 thousand, with 90 per cent. polynuclears).

"The next day the patient complained of some pain in his throat and presented a picture of peracute pharyngitis. The question came up whether this condition, the only positive condition found, might account for his hyperleucocytosis and fever. The patient was re-examined often twice daily, and the whole clinical picture continued most baffling.

"In the morning the patient was bright and cheerful, but towards evening there was well-marked depression. He ran a continuous high leucocyte count and an irregular febrile movement. He complained of no pain, and it was only towards the end of the first week that I detected tenderness on jarring in the right lobe of the liver in the axillary line. Later he developed slight tenderness high up and deep in the abdomen in the epigastric region, as well as tenderness on jarring in the left side of the chest in the region of the spleen. But for these few signs repeated physical examinations were negative.

"Gradually I came to the conclusion that there might be a suppurative process in the retroperitoneal glands behind the lesser omental bursa, or perhaps a localized peritonitis in the lesser sac.

"After going off service June 15, the condition continued about the same, and Dr. Buerger made an exploratory incision, and discovered thereby the nature of the malady, and cleared up many of the obscure symptoms as well as many of the points in the history which had been so misleading."

After the operation the patient continued to run an irregular temperature and a high leucocyte count, of 30,000 to 60,000, with 92 per cent. polynuclears and 1 per cent. eosinophiles. About two weeks after the operation the first nodule appeared along the right brachial artery. A week later a nodule appeared along the left brachial artery; then another appeared on the forehead. He left the hospital, and on his return the picture was that of a typical uremic condition. He also had a number of hemorrhages from the urinary tract, complicating the picture. You might summarize the case as irregular distribution of pain in the extremities and in the abdomen, with an irregular high temperature and a high leucocytosis, and extremely varying symptoms otherwise. In one of the cases reported by Lamb a high eosinophile count was regarded as a useful point of differential diagnosis. This was not present in this case. Blood cultures and all other laboratory examinations were negative. It is also important to note that this case was admitted to the hospital as an acute abdominal condition and was operated on for it. This also happened in two of the cases which have been reported. It is also interesting that the diagnosis was made during life. This was done in two other cases from the examination of the excised nodules.

Dr. Baehr: The only thing that might indicate the portal of entry of the infective agent in this condition was that the man repeatedly had attacks of tonsillitis of a peculiar character. At times the tonsils looked almost like those of Vincent's angina. Cultural studies were made, both from the lesions excised at operation, and from the tonsils, and blood cultures were made during life, both aerobic and anaerobic methods being used, but without result. In addition to the usual Veillon method of anaerobic culture, the Noguchi method for cultivating the spirochæte and the filtrable viruses was employed.

DIGESTIVE CAPACITY OF SPLENIC ADULT MESENCHYME AS FACTOR IN TUMOR DESTRUCTION

VERA DANCHAKOFF, M.D.

(From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director)

The phagocytic and digestive activity of the mesenchyme is not an activity discovered anew. Time and again observations have been recorded on the ingestion of organic and organized matter within the multicellular organism by various types of mesenchymal cells or by their cellular derivatives. Not the potency of the mesenchyme to digest in general, but the potency of the adult splenic mesenchyme to kill and to digest a living heterogeneous tumor cell is the new fact brought up by the study of the interrelation of the adult splenic mesenchyme of the chick and certain mammalian tumors growing together in the chick embryo. Mouse and rat sarcomata do not grow in an adult chick; certain of them easily grow in the allantois of the chick embryo. However, the factor which inhibits the growth of the mammalian tumor in the adult chick remains unknown. It is of great interest, therefore, to study the growth of tumor cells associated with various tissues of an adult chick in a medium in which both of the tissues, if planted independently, would give abundant growth. Such a medium is the chick allantois, and the results obtained by growing Ehrlich mouse sarcoma associated with adult splenic tissue is the object of this demonstration.

A graft of tumor alone will give in the allantois a good-sized growth on the fifth day. A graft of tumor and spleen thoroughly mixed before grafting, will also result in a good growth; but the growth will consist of splenic tissue practically alone, of its mesenchyme, and of its cellular derivatives, which in the allantois are granuloblasts and granular leucocytes. Only with the greatest care will one be able to discover in a graft of five days a few tumor cells. These are found to be encircled by a wreath of mesenchymal cells, as seen in Fig. 1. *A* is a tumor cell with a three-lobed nucleus which, though retaining its structural characteristics, does not present a healthy appearance. From a study of similar tumor cells in grafts of five days' growth and more, it is not possible to draw any conclusion as to whether such cells are, or have been, alive while being surrounded by the mesenchymal cells; neither is it possible to discover their immediate future. Only a study of the earlier grafts of tumor mixed with adult spleen will convince us that the few tumor cells found in a mixed graft after five days' growth, similar to that illustrated in Fig. 1, are the last remnants of a focus of a rapidly growing tumor, and that they will disappear, as the whole focus has disappeared.

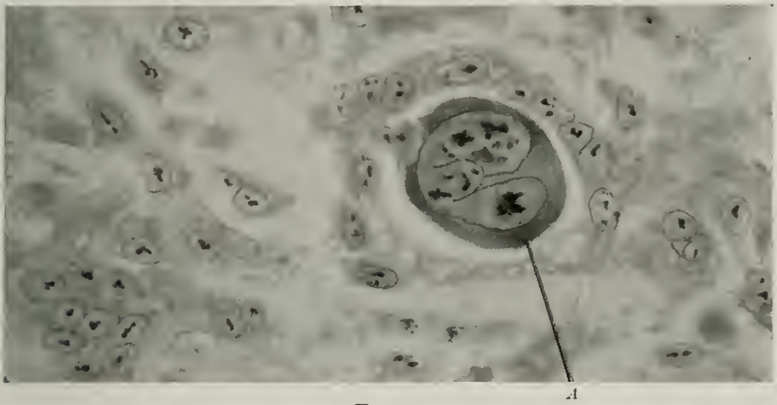


FIG. 1.

In a graft of four days' growth we find as a rule besides the splenic tissue small tumor foci, either surrounded by the mesenchyme of the adult spleen, or intimately intergrown with the splenic tissue. Such a focus is seen in Fig. 2. All the small dark spots are tumor cells, and, what is of great interest, a great number of them are found in vacuoles surrounded by a syncytium of mesenchymal cells. Numerous encircled tumor cells are found to be in a state of disintegration. A whole series of changes, from a healthy-appearing tumor cell to a small block of structureless protein, can be easily traced. The study of similar preparations, hundreds of them, suggests that the tumor cells encircled by a wreath of mesenchymal cells, are gradually losing their structure

—their cellular structure first, their chemical structure finally—and that they completely disappear as such. The tumor cell is transformed into a block of structureless protein; and the latter gradually undergoes further changes which result in the complete splitting of the protein. This process of digestion of tumor cells is accomplished within closed vacuoles surrounded by mesenchymal cells.

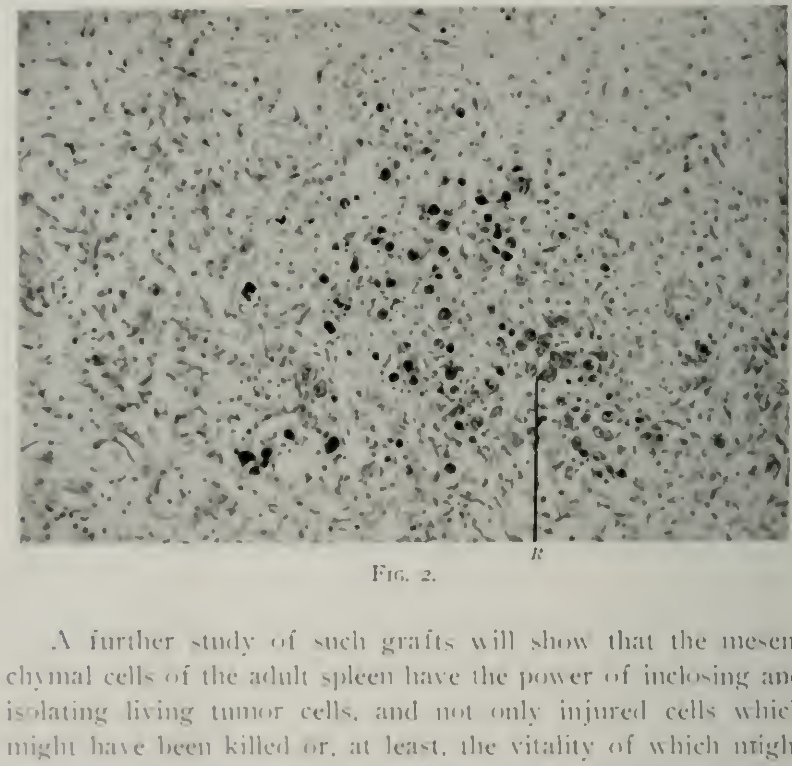


Fig. 2.

A further study of such grafts will show that the mesenchymal cells of the adult spleen have the power of inclosing and isolating living tumor cells, and not only injured cells which might have been killed or, at least, the vitality of which might have been lowered, either by mechanical manipulation during grafting, or by the action of certain proteolytic enzymes known to be present in the splenic tissue. In other words, the tumor cells are attacked not because of the inertness of their metabolism, but because of a special positive tropism of the adult splenic mesenchymal cells toward these particular tumor cells. A closer study of preparations similar to that illustrated in Fig. 2

shows that tumor cells which have undergone the greatest changes are invariably found in the periphery of the focus, and that besides an intermediate zone, in which numerous tumor cells are found in vacuoles with less pronounced changes, there is in the center of the focus a region (*R*) in which the tumor still exhibits its normal healthy texture and in which tumor cells continue to proliferate. And what is even more remarkable, proliferating tumor cells are also found in vacuoles surrounded by mesenchymal splenic cells. Living proliferating cells, therefore, and not merely injured ones, are surrounded by mesenchymal cells, or living tumor cells already in a vacuole may still proliferate for a certain length of time. The other tumor cells, some of them in the form of structureless protein, others showing unmistakable signs of degeneration, might therefore also have been surrounded while still alive and healthy.

In still earlier stages of three days' growth or a little over, the tumor foci are seen to be of a more considerable size with many more healthy cells, and with many more mitoses. At the periphery of such a focus, however, there already exists a zone, though a narrow one, in which the digestion of tumor cells is already taking place. Here tumor cells are cut off by the mesenchymal cells, surrounded and submitted to intracellular digestion —intracellular, because the vacuoles in which the tumor cells undergo the process of digestion are surrounded by an uninterrupted capsule of mesenchymal cells. The ingestion followed by the digestion of the tumor cells taking place at a higher rate in comparison with their proliferation, fewer and fewer healthy cells will remain in the tumor focus, until the whole graft will contain but a few of them, and finally none.

The process of digestion of the tumor cells is illustrated in Fig. 3. A tumor cell in mitotic division within a vacuole (*A*) is seen, as well as a number of other tumor cells undergoing gradual changes which result in the final disappearance of the cells. The tumor cell (*B*) has its cytoplasm vacuolized in a very characteristic way. The cell (*C*) is indented at its periphery, thereby illustrating how the vacuoles are opening and their contents are washed out, dissolved, and mixed with the contents of the vacuole.

Cell *D* is very much shrunken, with a hardly recognizable structure of its nucleus. *E* is just a small block of structureless protein, the only remainder of the previously living tumor cell.

If there still remains any doubt as to the digestive activity of the adult mesenchymal cell being the deleterious factor of growth inhibition, or rather of destruction of an actively and rapidly growing tumor in a mixed graft of tumor and adult spleen, two other arguments may add evidence to this contention. Grafts of tumor mixed with splenic tissue of chicks ready to hatch, in which all the cellular elements including the small lymphocytes are already differentiated, grow just as well as when grafted in a mixture with spleen of earlier embryos or with any other tissue.

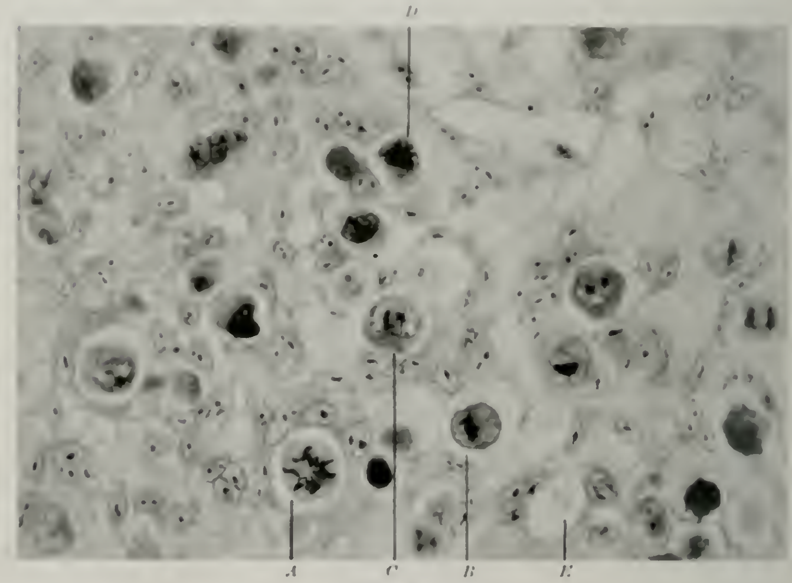


FIG. 3.

On the other hand, in grafts of tumor and adult spleen not mixed together, but grafted in the allantois side by side, a destructive zone will develop only at that part of the circumference of the tumor which is adjacent to the splenic tissue, and at the time when both tissues come to touch each other.

From all the evidence brought forward, it is obvious that the determining factor of the check of tumor growth in the mixed graft of tumor and adult spleen is the intraprotoplasmic digestive power of the mesenchymal cell, and certainly not an injurious effect of any other kind of cells which might be present in the grafted splenic tissue; nor is this check effected by a general resistance of the embryo which might have been produced by the introduction of any other kind of cellular elements. The biological process by which the adult mesenchymal cell ingests and destroys a tumor cell is easily traced and studied in the various stages of growth of the mixed grafts.

Discussion:

Dr. Wood: The phenomena described by Professor Danchakoff are most interesting, and illustrate some of the purely biological phases of tumor investigation which lead us to a proper understanding of the lives of cells, even though they do not promise practical approach to the cure of cancer. The various implications and limitations of this work are worthy of full discussion, and I should like to call attention to a number of points:

In the first place, the work has been done with one mouse tumor only, the Ehrlich mouse sarcoma; hence other types of tumors must be tested before generalizations can be safely made.

The assumption that the "determining factor in checking growth is the intraprotoplasmic digestive power of the mesenchymal cell" should receive careful consideration. This means that ferments destroy living cells. The general belief has been heretofore that the living cell, for example, that of the gastro-intestinal tract, resisted very successfully the attack of powerful ferments and succumbed only after its vitality had been seriously impaired. Rous' demonstration that living tumor cells resist tryptic digestion so that they can be freed from their stroma by submitting them to the action of a suitable digestive mixture is also of interest in this connection. Opie's demonstration that splenic tissue of the hen has practically no proteolytic power in neutral solution also throws doubt on the assumption that the phenomena described are digestive. To validate a new and far-reaching opinion on the morphology of the moderate number of tumor grafts studied leaves a large burden of proof to be assumed by the proponent.

The unquestioned checking of the tumor, as shown by this experiment, means, until it is explained otherwise, only that the Ehrlich mouse sarcoma will not grow in adult chicken spleen, which, as Professor Danchakoff says, has long been known. When the Ehrlich sarcoma is transplanted to the spleen of a three or four months chick, no phagocytosis occurs. The cells rapidly perish and are absorbed at such a rate that no visible tissue reaction follows. On the other hand, may the killing of the tumor cells not be due to causes other than ferment action? An equally justifiable assumption would be that the rapidly growing tumor cells are destroyed not by ferments but by being excluded from participation in the general food supply by the surrounding syncytial mass of mesenchymal cells. The splenic cell being on the outside would have first choice of all food, and the tumor cell would thus be deprived of sufficient nutrition. The presence of mitotic figures in the engulfed tumor cells is suggestive of an agonal effort of the cell to increase its absorptive surface by division. Such division figures are seen in spontaneously receding tumors. Their presence does not guarantee the health of the cell, nor does their absence its inability to grow further. This starvation hypothesis is strengthened by the fact that if the tumor and splenic grafts touch only at the periphery, the action in the tumor cells is extremely local, being limited to the point of contact, and the remainder of the tumor grows as if there were no spleen present. Ferment action might be expected to be effective at a distance a few microns from the cell, but instead it is only the engulfed tumor cell which is affected. In this connection the phagocytosis by leucocytes of living cells which can be observed *in vitro* in blood drawn from a person suffering from malaria is instructive. The pigment in the engulfed parasite may remain in active motion for some hours, but the cell membrane remains sharply defined against the somatoplasm of the leucocyte. Some time after the pigment activity has ceased the membrane fades and the cell undergoes digestion. Certainly the leucocyte possesses ferments, but there is no proof that they act before the death of the engulfed cell. It would seem more conservative, therefore, for Professor Danchakoff to show that the tumor cells are not killed by other means before postulating a death due to ferment activity.

It might also be wise before assuming the destruction of all the tumor cells to transplant into mice some of the double grafts at a period when it might be deduced from morphology alone that all the tumor cells had disappeared. The allantois is not an optimum soil for the growth of mouse tumor, as Stevenson showed, even when spleen is not present, and the biological variability of transplanted tumors is very great as all who have worked with them know.

The observations made by others on tumors either spontaneously receding or being absorbed after radium treatment point strongly to the fact that connective tissue cells are actively phagocytic only of dead tumor cells.

The inhibition of tumor growth by adult spleen, as observed by Professor Danchakoff, explains one phase of the phenomena of resistance to tumor growth but does not confirm the hypothesis advanced by Dr. Murphy of the Rockefeller Institute, but recently shown to be generally untenable. Dr. Murphy's theory was that the lymphocytes inhibited the growth of the tumor. In his opinion, this action was general; that is, the animal's own lymphocytes might offer resistance to the tumor; but as was shown by Apolant and by Woglom it is impossible to produce tumor immunity with an animal's own tissues, and Dr. Murphy himself has lately called attention to the difficulty of explaining how tumors proliferate so freely in the lymph-nodes if the lymphocytes carry an antagonistic material.

Dr. Danchakoff: I think it is very easy to replant these grafts of tumor and spleen grown on chick back into mice. I would like to add that the digestive power of the mesenchyme, though restricted to the particular medium, and especially to certain kinds of tumor, has been so clearly illustrated in other cases that it might have a more general meaning. If all the facts relating to the digestive capacity of tissues in general were brought together we might appreciate with a better understanding the general resistance of the organism against the proliferation of a foreign tissue in it.

DIFFUSE CARCINOMA OF STOMACH

L. C. KNOX, M.D.

A young woman, aged twenty-three years, was admitted to the service of Dr. L. F. Frissell at St. Luke's Hospital, on March 22, 1919. Four months previous to admission she had first suffered from indigestion, which began about thirty minutes after the ingestion of food and lasted for one to two hours. The symptoms were eructation of gas and distension of the stomach. There was also a moderate amount of pain which was increased by the taking of food; this was localized over the stomach region and did not radiate to the lower portions of the body. Latterly, she had vomited a few times, but had never noticed any blood in the vomitus. She had been constipated and had lost her appetite, and thought she had lost a good deal of weight. There were also general symptoms of nervousness, headache, insomnia, cardiac palpitation, dyspnea, and fatigue on exertion.

Her previous history was unimportant; she had always been well up to the onset of the present illness.

Examination of the patient showed a very poorly nourished white woman with marked loss of weight. The skin was not jaundiced. There was a mass in the epigastrium, extending to the left and palpable about 5 cm. below the costal margin, with a very distinct lower edge; the mass moved with respiration.

The temperature was 99° F.; the pulse 80–130.

The laboratory reports showed that the hemoglobin was 66 per cent.; the red cells numbered 3,700,000; the white cells, 6,000; the polynuclears were 70 per cent., the lymphocytes 24, and the eosinophiles 6. The Wassermann reaction was negative.

Examination of the urine showed acetone, diacetic acid, and indican. The blood pressure was: systolic 120; diastolic 75.

In the fasting state the stomach was found to contain 35 c.c.; the fluid contained no acid, either free or combined; blood was present. After a test meal, 50 c.c. were obtained; this also was wholly free from acid, and contained much blood.

Examination of a stool showed the presence of trypsin, but no blood.

X-ray examination of the stomach on March 26, 1919, showed that an opaque meal passed immediately out of the stomach. Another examination on April 3, showed that: "the meal passed very rapidly through the stomach, leaving just a faint outline of the stomach wall, especially at the pyloric region. There was distinct delay in the esophagus, showing moderate dilatation. The duodenum was well filled, and the meal scattered rapidly through the small intestine. The findings were typical of specific infiltration of the stomach wall."

Three doses of neosalvarsan were given at this time, but without relief.

On April 23, an exploratory laparotomy was done by Dr. F. S. Mathews, and there was found to be a very contracted tubular stomach adherent to the under surface of the liver by fresh adhesions. The duodenum, the pylorus, and one inch of the distal end of the stomach were normal. From this point, which was marked by a hard indurated border, the stomach walls were greatly thickened and the stomach was contracted. The walls were very hard, suggesting carcinoma. A few hard nodules were found in the omental fat, and were sent to the laboratory for examination; microscopical examination of these showed the presence of carcinoma.

Despite the performance of a jejunostomy, the patient rapidly grew more emaciated, suffered severe pain in the epigastrium, and died two weeks after the operation and six weeks after admission to the hospital.

The autopsy showed nothing of importance except in connection with the stomach. The gastrohepatic omentum and perigastric fat showed extensive infiltration with the neoplasm. The growth began at the cardia and extended under the lesser curvature, stopping abruptly about 3 cm. above the pyloric opening. The lesser curvature was very much thickened; the omentum was firmly fixed to the greater curvature, and only a small portion of the fundus remained free of the growth. The stomach was much contracted, measuring about 10 cm. in diameter (Fig. 1). The liver was small and its surface smooth except for such portions as were originally adherent to the stomach.

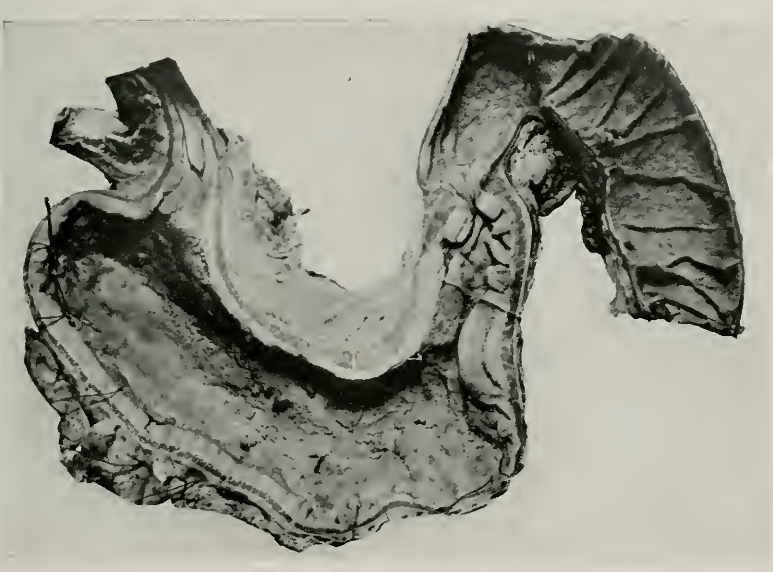


FIG. 1. Thickened walls and contracted lumen with no ulcer or mass.

Microscopical examination showed that the mucous membrane of the stomach was smooth and velvety, without any noticeable ulceration; the walls were very much thickened, and very hard and fibrous. Microscopically the mucous membrane was still fairly well preserved over much of the stomach, though in a few areas there had been either post-mortem degeneration or loss of substance during life. The site of the cancer was chiefly in the submucosa (Fig. 2), although all the muscularis was thoroughly infiltrated with tumor cells (Fig. 3). The perigastric fat was also diffusely involved.

The case is interesting not so much because of the rarity as because of the early occurrence of the disease.

Large series of cases show that only about 0.1 to 0.2 per cent. of gastric carcinomata occur under the age of 20, and that even up to the third decade they are very infrequent.

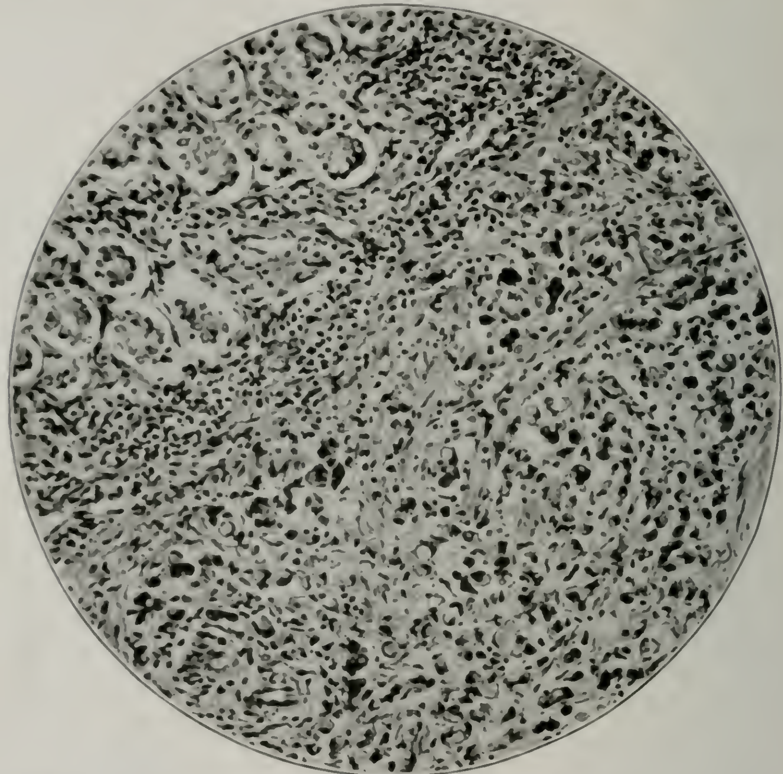


Fig. 2. Section of mucosa and submucosa showing the latter diffusely infiltrated with carcinoma cells, while the former remains relatively normal. High power.

De la Camp (quoted by Keene), states that in 9,906 instances of malignant gastric tumors, there were 19 under 19 years of age.

Smithies and Oehsner mention only one under 19 years among gastric carcinomata, and only 9 occurring before the age of 30. Even among the malignant growths of childhood and early adult life, the stomach is one of the less frequent sites. Warthin's statistics showed only two before the thirtieth year among 195 malignant tumors. His youngest case was 14 years of age.

Merkel, however, shows that they have probably been seen earlier, reporting one in an infant of 5 weeks and two at 13 years. According to Williams the youngest authenticated case of a gastric carcinoma is that of Moore. It occurred at 13 years.

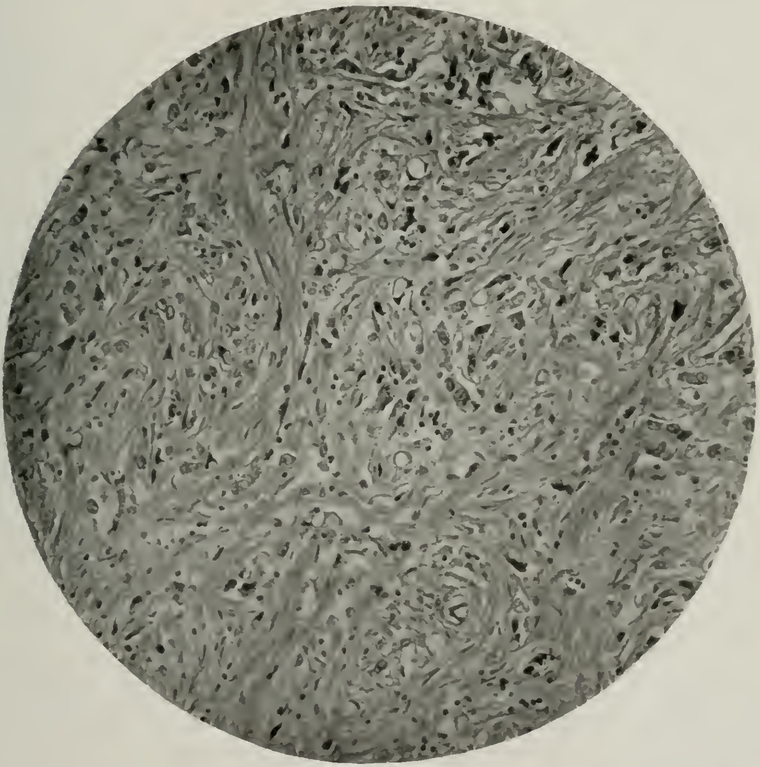


Fig. 3. Portion of muscular coat of stomach showing diffuse invasion with carcinoma cells.

In any case such a tumor is certainly rare at the age of twenty-three, and the diagnosis of it is correspondingly difficult.

The diagnosis lay between syphilis, linitis plastica, and carcinoma of the stomach. There was no history of syphilis, and no Wassermann reaction was given: this while not absolutely excluding syphilis rendered it doubtful. The diagnosis between linitis plastica and scirrhous carcinoma of the stomach is very difficult clinically. In both, the stomach is rigid, the food passes rapidly, blood is frequently present, and hydrochloric acid is absent; lactic acid is often present. Rapid emaciation and vomiting occur in both conditions. Age has often been considered as a differential point, but fails in this instance.

Ascites occurs in linitis and also in polyserositis, which may occasionally by a great thickening of the surface of the stomach give rise to symptoms closely resembling those of linitis and of carcinoma.

In general, linitis is a much rarer disease than scirrhous carcinoma. Where the disease is very chronic, lasting from ten to fifteen years, the history differentiates; but in the rapidly progressing cases the diagnosis has usually been made, as it was in this case, by microscopical examination of material obtained by exploratory laparotomy.

References

A very complete review of the non-malignant forms is given by Kurt v. Sury. Beitrag zur Kenntnis der totalen, einfach entzundlichen Magenschrumpfung und der fibrosen Polyserositis (Zuckerguss), *Arch. f. Verdauungs-Krankh.*, 1907, xiii, 1.

Brunig and Schwalbe: Handbuch der allg. Path. d. Kindesalters, Wiesbaden, 1912, p. 422.

Krompecher: Zur Anatomie Histologie und Pathogenese der gastrichen und gastrointestinalen Sklerostenose. *Ziegler's Beitrage*, 1910, xlix, 384.

Williams: Natural History of Cancer. New York, 1901.

Keene's System of Surgery, iv, 1158.

Smithies and Ochsner: Cancer of the Stomach. Philadelphia, 1916, p. 28.

Warthin: The Occurrence of Malignant Neoplasms in the Young. *Arch. Int. Med.*, 1915, xv, 444.

Brinton: Lectures on Diseases of the Stomach. Second Edition, Philadelphia, 1865.

N. Moore: *Trans. Path. Soc.*, London, 1885, xxxvi, 195.

Discussion:

Dr. Manges: I have a case at Mount Sinai Hospital, a young man of 27 years of age, with carcinoma of the stomach. The only other case of malignant disease of the stomach at an early age that I can recall was a sarcoma of the stomach, in which bleeding was rather a prominent feature. Dr. Knox made a reference to the differential diagnosis of syphilis of the stomach. I am glad that that diagnosis was wrong, because it strikes me that it is now extremely fashionable to make the diagnosis of syphilis of the stomach; and in spite of the recent article from the Mayo Clinic, I think that you will find that, even if the patient has a positive Wassermann reaction, it does not mean syphilis of the stomach.

PRIMARY INTESTINAL TUBERCULOSIS

MAX PALINSKY, M.D.

(*From the Pathological Laboratories of Bellevue and Allied Hospitals; Director, Dr. Douglas Symmers*)

There seems to be an opinion current among certain surgeons that primary or so-called surgical tuberculosis of the intestine is not an uncommon occurrence, and, based on this opinion, many surgeons have actually carried out extensive resections.

Anatomically, there are two well-recognized varieties of intestinal tuberculosis. One of them invites surgical interference. This lesion is characterized by the presence of a chronic productive inflammation of the cæcal region and even of the greater portion of the ileum. It eventuates in massive thickening of the intestinal wall and in obstruction or even occlusion of the lumen. The second variety consists in solitary or multiple, discrete or fused tuberculous ulcers corresponding, as a rule, to the distribution of the lymphoid tissues of the gut.

Our attention at Bellevue Hospital was recently focused on the subject as a result of the removal at operation of the terminal 25 cm. of the ileum, the cæcum, appendix and lower fourth of the ascending colon. Anatomically, a massive ulcerative lesion was found, the naked eye appearance of which suggested the diagnosis of tuberculosis. Microscopic examination, however, showed the presence of an adeno-carcinoma.

In order to determine the incidence and distribution of tuberculous lesions of the intestine, with particular reference to the advisability of surgical interference, I undertook a systematic examination of 6,000 consecutive autopsy protocols on file in the pathological laboratories at Bellevue Hospital. No example of chronic hyperplastic tuberculous enteritis was encountered in the autopsy cases. Since the establishment of the laboratory fourteen years ago, however, six examples of so-called surgical tuberculosis of the intestine have been encountered among approximately 33,000 specimens received from the various operating rooms in the hospital. Of the six, three represented examples of chronic hyperplastic tuberculosis of the ileo-cæcal region.

Of 6,000 consecutive autopsies performed at Bellevue Hospital between 1904 and 1919, 285 cases showed tuberculous involvement of some portion of the intestinal tract. The percentage of individuals dying of chronic pulmonary tuberculosis with concomitant involvement of the intestine has been variously estimated, by some as high as 80 per cent. At Bellevue Hospital, 46 per cent. of such patients showed tuberculous lesions of the gut. We are not so much interested in this aspect of the problem, however, as in its converse—namely, the percentage of individuals with intestinal tuberculosis who show tuberculous involvement of the lungs or other organs. Of the 285 cases just referred to, only five, or 1.75 per cent., failed to reveal pulmonary tuberculosis. Of these five, two, however, showed tuberculosis of some other part of the body; one tuberculous peritonitis and the other tuberculous mesenteric lymph nodes, thus leaving only three cases in which the intestine was alone involved (1 per cent.). Of the 285 cases, the distribution of the tuberculous lesions was as follows:

Small intestine	180 cases or	63 per cent.
Large intestine	116 cases or	41 per cent.
Ileum	62 cases or	21 per cent.
Caecum	26 cases or	9.1 per cent.
Appendix	7 cases or	2.8 per cent.
Duodenum and rectum	1 case each or	0.3 per cent.

all of them being of the ulcerative variety.

CONCLUSIONS

First, that primary intestinal tuberculosis is an exceedingly rare condition and that before such a diagnosis be made, the lungs should be thoroughly investigated by every means available; secondly, in 37 per cent. of all cases of intestinal tuberculosis, more than one part of the gut is involved. Not infrequently the ulcerative lesions occupy both colon and small intestine, so that the operative removal of any portion of the gut for tuberculosis should be approached with the greatest caution.

Discussion:

DR. MOSCHCOWITZ: May I ask whether you investigated the incidence of tuberculosis of the mesenteric lymph nodes?

DR. PALINSKY: All cases that showed any tuberculosis of the intestine without involvement of the lungs were put down. We took 6,000 autopsy records and looked for tuberculous involvement of the intestine and worked back from that to find how many cases showed involvement of the lungs or mesenteric nodes. There was only one case in which the mesenteric nodes were involved without any lung involvement.

A CASE OF THYMOMA

P. KLINGENSTEIN, M.D.

The case of primary tumor of the thymus which I have the opportunity of presenting to-night is of unusual interest both because of the rarity of the condition and of the opportunity afforded for a discussion of this type of neoplasm.

E. F., aged 20, entered Mount Sinai Hospital in July of this year on the service of Dr. Lilienthal, to whom I am indebted for placing these records at my disposal. His chief complaints were pain in, and swelling of the whole left upper extremity for one week. His family and past history were irrelevant. The positive findings on admission were a mild grade of anæmia, and the local condition, which consisted of a brawny edema of the whole left upper extremity including the neck on the same side. There were some moderately enlarged cervical, axillary, and supraclavicular lymph nodes. In addition the brachial vein was thrombosed and easily palpable. *X*-ray examination showed an infiltration of the right lung at the extreme base. The patient remained in the hospital ten days and left greatly improved. Both the edema and adenopathy had largely subsided. At that time a tentative diagnosis of mediastinal tumor was made.

About one week later the patient was readmitted to the hospital upon the medical service of Dr. Oppenheimer; complaining of a mass of the right chest wall, swellings of the jaw, and of several nodular swellings upon the head. Physical examination then revealed an anæmic young man with dyspnea and orthopnea. There were in the scalp about half a dozen irregular fixed nodular swellings varying in size from a pea to a walnut. The right lower portion of the chest wall showed the presence of numerous firm tender swellings attached to the ribs. Examination of the chest showed a wide area of paramanubrial dulness, with flatness and diminished breath sounds over both lower lobes posteriorly. *X*-ray examination showed a dense shadow on both sides of the mid-line anteriorly and in addition fluid at both bases. The Wassermann reaction was negative. Blood count showed only a secondary anæmia. *X*-ray examination of long bones and skull showed no involvement. During his stay in the hospital the patient developed more nodules and succumbed about three weeks after his second admission. The clininical diagnosis was a mediastinal neoplasm. At the autopsy the findings were briefly as follows:

Subcutaneous masses were palpable in the scalp, over the forehead and chest wall. A large well-defined tumor mass occupying the entire upper portion of the anterior mediastinum was seen between the posterior surface of the sternum and pericardium, filling in the region normally occupied by fat and the remains of thymic tissue. It was roughly triangular in shape with the base resting upon the great vessels and pericardium. The apex extended upwards into the tissues of the neck. Its greatest length was 15 cm., the greatest breadth and thickness 8 and 5 cm., respectively. Its relations to the neighboring organs were as follows: Anteriorly it was easily separated from the posterior surface of the sternum, being enveloped by reflections of the pericardium and pleuræ as is the normal thymus. On both sides it was practically free, its base resting upon the pericardium. Posteriorly it was intimately connected with the structures of the posterior mediastinum, especially the great vessels and the lower portion of the trachea which it narrowed considerably; also with the hilums of both lungs, along which the tumor seemed to grow infiltrating along the bronchi of the left lung and into the parenchyma of the right as though growing by lymphatic extension. The tracheo-bronchial lymph nodes as well as those deep in the hilus of the lungs were small, well encapsulated, and appeared free of tumor tissue. The tumor was dense in consistency. The cut surface was not absolutely homogeneous but consisted of some coarse strands of fibrous tissue between the more uniformly gray appearing cellular substance. The other organs of the body were uninvolved.

Microscopically the great mass of tumor tissue consisted of cells resembling those found in the thymus, in that it was comprised of small round cells of uniform size and possessed of large deeply staining nuclei lying in the meshes of a fine reticulum. There were some small capillaries present. A very thorough search failed to reveal any Hassal corpuscles.

To state definitely that a tumor originates in the thymus one should inquire first as to its position, second, its form, third, its relationship to the histological elements normally found, and finally its structure. While the position of the mass is useful, as in this case, in determining its origin, it must be remembered that this type of tumor not only invades the anterior mediastinum, but may involve adjacent structures. Still less can we rely on the form of the growth except in those cases in which the tumor actually corresponds to the anatomical limits of the thymus, as in our case, or in which the gland is the seat of a hyperplasia or a pseudoleukæmia. Many have held that to find remnants of thymic tissue in the tumor is sufficient to establish its origin. This has been disproved by Friedleben who has shown that Hassal's corpuscles diminish rapidly after the first year of life, and that a neoplasm may invade thymus rests and in this way lead to false inferences. In this case the differential diagnosis, so to speak, lies between a lymphosarcoma of the thymus, or thymoma, and a lymphosarcoma originating in the lymph nodes of the mediastinum. In favor of the former is first the shape and position of the mass, and secondly the fact that the lymph nodes encountered are small and encapsulated. Then again the lymphosarcomas of the mediastinum are usually more nodular; and finally the cells seen in this tumor are not like those of ordinary lymphosarcomata, but appear more like normal cells seen in the thymus or lymph nodes.

Before discussing primary thymus tumors it is important to consider the developmental history and histogenesis of the gland. The thymus is developed from the epithelium of the third and fourth pharyngeal pouches as a paired anlage. This first becomes a thick walled branched cylindrical tube much like a tubo-alveolar gland. The lumen disappears with the subsequent formation of the thymus cord. This thickens at the caudal end forming the body of the thymus. The entire anlage migrates caudally, the body more than the cephalic portion. The two separate anlagen fuse and are separated by a thin fibrous septum. The epithelial masses become invaded by growing lymphocytic tissue and blood vessels. The structure of the thymus is briefly as follows: The gland is divided into lobes and lobules by fibrous septa; the lobules are differentiated into a cortical and medullary zone, the cortical substance appearing like dense lymphoid tissue. The closely packed lymphocytes lie within a supporting reticulum, the latter consisting of stellate anastamosing cells. The medulla is made up for the most part of a supporting framework with masses of concentrically displaced flattened cells, the corpuscles of Hassal. As to the histogenesis of these cells there is little question that the reticular cells and those of Hassal's corpuscles are of epithelial origin. In regard to the thymus cells there are two views—the one supported by Maximow and Hammar, that these cells are immigrated thymus lymphocytes and derived from the mesoderm, the other held by Stoehr that they are simply modified epithelial elements. Recently Danchakoff has presented more convincing evidence that the mother cell of the thymus cell is a true lymphoid hemocytoblast.

One can readily understand that the classification of primary solid tumors of the thymus depends upon whether we hold them to be derived from mesodermal or entodermal elements; and with this uncertainty still confronting us along with the rarity of the condition, it is little wonder this class of tumor has been classified with the nondescript title "thymoma."

Von Schridde writing in Aschoff's text-book does not make the deciding step necessary for a classification but calls them all malignant tumors: "Bösartige Geschwülste." The name "thymoma" as introduced by the French authors is again a collective term including all malignant growths of the thymus. If the gland is an organ composed of lymphocytes and epithelial cells it naturally follows that it can be the seat of sarcoma or of carcinoma.

More recently Dr. Ewing in his work on neoplastic diseases has classified tumors of the thymus as (1) lymphosarcomata, or thymomas, thereby limiting the scope of this term as tumors arising from round, polyhedral, or giant cells and (2) carcinomata arising from the reticulum. The same author holds that the round cell tumors of the thymus differ from those of the lymph nodes and suggests that the reticulum cells may be the chief source of the neopiasm.

Primary tumors of the thymus are comparatively rare. Rubaschow reviewing the literature in 1911 was able to collect 69 cases up to that time; of these 15 were doubtful leaving only 54 authentic cases. Of this number 52 proved to be sarcomata with 19 uncertain as to the point of origin. Of the 33 remaining cases lymphosarcoma was present in 19, other forms of sarcoma in 11. The age incidence of these 33 cases was as follows: Up to 25 years, eighteen; between 25 and 40 years, eight; more than 40 years, seven. Carcinoma of the thymus is much more rare. This whole group of tumors is rapidly malignant, metastasizing along the lymphatic channels and usually involving distant organs. In 1908 Mandlebaum and Celler reviewing the literature of myasthenia gravis found this interesting condition associated with thymic tumor in no less than eleven cases. There was no evidence of myasthenia in this case.

Our interpretation of this case is that it represents a primary lymphosarcoma of the thymus.

A CASE OF THYMOMA

JAMES EWING, M.D.

The case I have to present I call thymoma for want of a better term, rather than from any positive conclusion that it belongs in this category. The specimen comes from a man thirty-nine years of age, who began to suffer a little over three years before his death from swelling of the cervical lymph nodes, which was the only symptom that attracted attention. He had suffered from these swollen nodes for about a year before any attention was drawn to his chest. Then it was thought he had a mediastinal tumor. He was treated by various internal methods for another year, when he reached New York, and here the presence of a mediastinal tumor was demonstrated. He arrived at the Memorial Hospital about three months before his death. At that time he showed traces of the original enlargements of the cervical lymph nodes. These were reduced by radium and *x*-ray treatment, but the thymic tumor persisted. It was somewhat reduced in size, according to the *x*-ray plates, during his stay in the hospital, but did not disappear. At the beginning of his stay in the hospital abdominal palpation indicated that he had some swelling in the abdominal region, and these abdominal signs increased rapidly, so that after a time it was possible to demonstrate that the pelvis was filled with a tumor. This continued to grow, and all during this period he suffered from progressive anemia. He had no specific signs of myasthenia gravis. He died with symptoms of asphyxia and with a cachexia which went with the progressive anemia. A point that should be emphasized is that for at least two years he was regarded as a case of Hodgkin's disease.

At autopsy quite a remarkable condition was present. The lymph nodes of the neck were not palpable. They were represented by small, pea-sized nodules, more or less sclerotic. In the region of the thymus was a solid, rather soft, very opaque, light yellow, but not distinctly lemon colored, tumor mass measuring 6 × 8 × 5 cm., capping the pericardium, composed of very numerous, more or less discrete nodules, surrounding a considerable portion of the trachea and the great vessels. The mucous membrane over several inches of the trachea and bronchi showed submucous infiltration. The main mass appeared in the abdomen and presented almost a continuous growth from the bottom of the pelvis, surrounding the rectum, running up in a continuous mass along the great vessels, adherent to the spinal column, surrounding the kidneys, but limited by the renal capsule, surrounding the pancreas, which ran through the tumor without any signs of compression, and running up into the nodes at the celiac axis. It is difficult if not impossible to determine the origin of this tumor. From the clinical standpoint the evidence is strongly in favor of a primary mediastinal tumor, because during the observation of the patient before he reached New York, attention had been specifically drawn to the presence of a mediastinal tumor, and this was quite easily demonstrable by the *x*-ray plate. It was only within the last three months of his life that the pelvic and abdominal tumors could be recognized. A careful anatomical study of the mediastinal growth gives only suggestive, but not positive, evidence that we have a primary thymic tumor. The next piece of evidence might come from the histological structure, but the tumor does not show the characteristic structure presented by some thymic tumors. That structure shows lymphocytes in a peculiar stroma in which giant reticulum cells are very prominent. The structure of this tumor presented a rather diffuse growth of cells larger than lymphocytes, with large nuclei, and with a strong tendency to fasten themselves to the strands of connective tissue making up the stroma. I am convinced that we are not dealing with a simple lymphosarcoma, either lymphocytoma or reticulum cell sarcoma, but I am not able to assert that the tumor arises from the thymus. I think that the clinical evidence and the anatomy of the disease favor the diagnosis of a tumor of the thymus. The structure does differ from that of a simple lymphosarcoma.

One has to recognize three histological structures in thymic tumors. One has been called by the French observers "thymic carcinoma." It is made up of polyhedral cells, often alveolar in arrangement, and without any doubt derived from the epithelial reticulum cells of the gland. There is another tumor made up of lymphocytes derived from the lymphocytes of the thymus, and properly regarded as the thymic form of lymphocytoma. There is a third group, concerning the nature of which I am not prepared to make any dogmatic statements. It is a very cellular and malignant tumor composed of cells that are rounded, irregular, larger than lymphocytes, with large hyperchromatic nuclei showing a tendency to attach themselves to the stroma with a certain polarity. That structure does not belong to lymphosarcoma. I am inclined to think that we have here to deal with a tumor derived from the reticulum cells of the thymus, but more anaplastic than the ordinary carcinomas of the thymus, and hence growing more diffusely. If this conclusion is correct, then there are two types of tumors derived from the stroma cells, which are epithelial in origin, and one derived from the lymphocytes. These very cellular thymic tumors have been described in the literature, and they have regularly disseminated widely and produced bulky growths.

Discussion:

Dr. Larkin: This is a difficult subject to discuss because of the rarity of the condition. In my collection I only have one specimen of a tumor of the thymus gland. That tumor has preserved the architecture of the thymus gland itself, though the gland is enormously increased in size. It is composed of a number of different tissues, which makes one conclude, when the whole is studied in serial section, that although it is a tumor of the thymus gland, it does not belong to the gland itself. In the first place, there is a large amount of connective tissue interlaced with fatty tissue, striated and smooth muscle are present, and there are large masses of cartilage and masses of blood, so that one would conclude that the tumor belonged to the dermoid type. On serial section one cannot find a vestige of normal thymic tissue. The individual from whom the tumor was removed came into the hospital suffering from pressure, asphyxia, and increasing edema, and with these symptoms she died. The tumor was an accidental finding. The tumor presented by Dr. Ewing brought a question to my mind. Were the long bones in this case examined? It is difficult, looking at the tumor as it is presented, to place it as a primary thymic tumor. The histological picture is difficult to interpret, and the extent of the metastatic deposit is so vast that I know Dr. Ewing himself has not made a definite diagnosis of a primary thymic tumor.

Dr. Baehr: The specimen presented by Dr. Klingenstein represents the first example of thymoma seen in almost four thousand autopsies at Mount Sinai Hospital. Microscopically, the tumor belongs undoubtedly to the group of lymphosarcoma or lymphoblastoma; the cells are much smaller than those seen in the ordinary lymphosarcoma, being more nearly the size of normal lymphocytes. However the tumor shows numerous mitotic figures, and there is no doubt of its malignancy. One interesting feature of the pathological condition is its method of invasion along lymphatic channels. It invaded the lung in the peribronchial tissue, but in addition worked through into the mucous membrane of the bronchi and extensively infiltrated the mucous membrane of the larger bronchi and of the trachea. Undoubtedly the narrowing of their lumen which it produced was responsible in great part for the marked dyspnœa and orthopnœa.

Dr. Moschcowitz: I am rather surprised to learn that thymomata are rather rare findings, especially in view of the fact that I have seen at autopsy at least half a dozen primary lymphosarcomata of the mediastinum. I would like to ask Dr. Ewing whether he believes that these tumors are of thymic origin. Certainly they have all the morphological characteristics of those that have been presented this evening, except that the characteristic thymic shape is absent. They infiltrate the lungs at the root along the course of the larger bronchi, and do not as a rule give rise to many metastases. Mediastinal tumors are certainly common cases in the wards of a hospital, and while a few are primary carcinoma of the bronchi, by far the greater majority are lymphosarcomata.

I would also like to ask Dr. Ewing whether he does not believe it possible that the growth in his case had multiple origins. Kaufmann describes a form of diffuse lymphosarcoma of the glands of the entire body, and it seems to me possible that Dr. Ewing's case is of this type.

Dr. Ewing: Dr. Klingenstein's case under the microscope impresses me as a straightforward lymphocytoma. I agree with all that has been said about the origin in my case. Frankly, I think it ought not to be classed definitely as a thymoma. Dr. Larkin suggested possible origin from the adrenals. I do not think that either the structure of the tumor, or the anatomy, bears this out. He also suggested the possibility of bone origin. The bones were not affected, as x-ray examination showed no change in them. Our chairman suggests very astutely a multiple origin. Very probably that would be the best place to put my tumor, as arising in the lymph structures of the thorax and abdomen, if it were not for the clinical history, which we cannot afford to ignore, that this man suffered for a year or two from thoracic and cervical symptoms, which I think indicates that the disease developed in the abdomen later. This is in accord with some of the symptoms which we know to accompany thymoma. They extend widely in various directions, up into the neck, for instance. In many respects the tumor has features which require us to cut it out from the ordinary category of lymphosarcoma. It seems highly desirable to subdivide the group of lymphosarcoma as far as possible. Frequently one can accomplish that subdivision with much greater certainty than I have been able to do here.

AN UNUSUAL CASE OF DIAPHRAGMATIC HERNIA

A CASE OF ACUTE PANCREATITIS, DUE TO CALCULUS IN AMPULLA OF VATER

H. F. POHLMAN, M.D.

(*From the Pathological Laboratory, Lenox Hill Hospital*)

The specimens presented are of interest not merely as pathological curiosities, but because they represent morbid conditions which were associated with unusual clinical symptoms, or with an absence of symptoms covering a long period of time.

The first specimen is from a case of diaphragmatic hernia occurring in a man sixty-three years of age, who was admitted to the hospital with a diagnosis of subacute intestinal obstruction of the transverse colon. During his life, previous to his last illness, he had suffered from no symptoms, and had never had the services of a physician. At operation the cause of the obstruction was discovered in a dense mass of adhesions which bound the colon to a hernial ring in the diaphragm. The patient survived the operation about twenty-four hours, dying of shock.

At autopsy, a hernial ring 8 cm. in diameter was found in the muscular portion of the right leaflet of the diaphragm, anterior to the opening for the vena cava. Through this opening a surprisingly large portion of the abdominal viscera had forced its way into the chest cavity. Occupying the anterior portion of the cavity, and reaching to the level of the second rib was a loop of colon, 25 cm. in length. On freeing the cavity of the loop of gut, the heart was found to be extremely misplaced to the left, the apex touching the left chest wall in the mid-axillary line. Closely pressed against the vertebral column were the lower and middle lobes of the right lung, both completely atelectatic and sinking in water. Directly anterior to the lung and to the right, the distal two thirds of the stomach and a part of the first portion of the duodenum presented, the constriction of the hernial ring causing it to assume the hour-glass form. By far the most interesting change occurred in the liver (Fig. 1). Roughly, about two thirds of the right lobe had been forced into the thorax between the stomach and the ascending limb of the colon in such a fashion that the gall-bladder which was within the chest faced directly cephalad for its entire length. The remaining lobes of the organ were united by flat, drawn-out pedicles of liver tissue. That portion of the organ within the thorax, presented an extensive hobnailed cirrhosis, induced, in all probability, by the chronic conges-

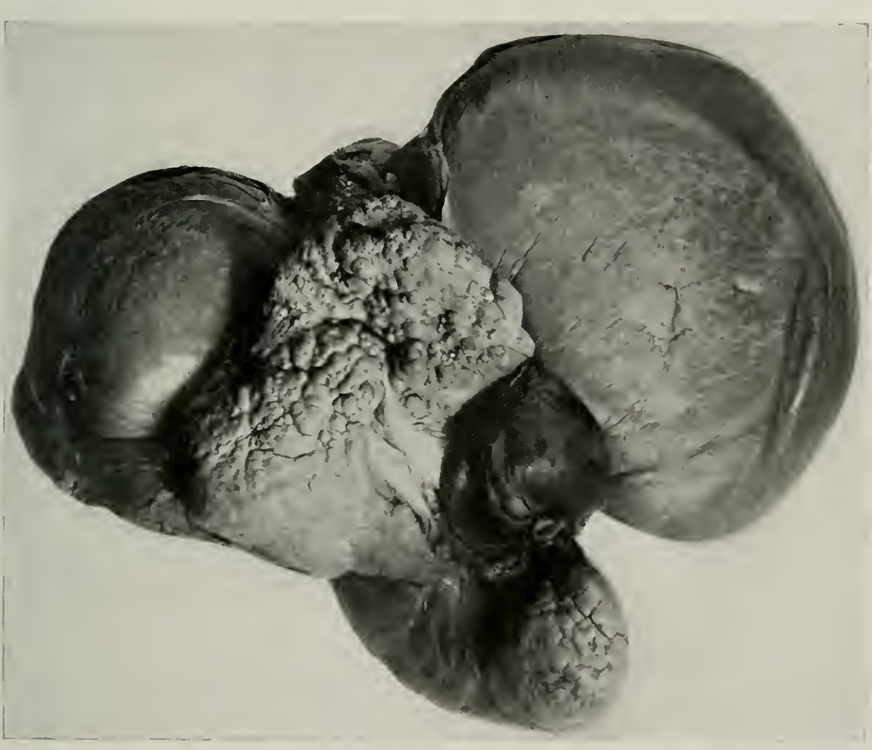


FIG. 1. Liver showing cirrhotic changes.

tion brought about by the hernial ring. The remaining portions of the liver showed no marked pathological changes.

The second specimen is from a patient aged forty-five, who was admitted to the hospital six months before her death, with the typical history and symptoms of gall stones. She was operated upon shortly after admission to the hospital, a cholecystectomy being performed. At the operation the cystic and common ducts were found to be patent. She developed a post-operative biliary fistula which refused to close except for short periods of from twenty-four to seventy-two hours. When the fistula closed the patient complained of abdominal cramps and became jaundiced. Having refused a second operation she was discharged from the service after two months' stay. Twenty-four hours before her death she was re-admitted with a history of unusually severe cramps accompanied by a sudden deep jaundice and marked collapse. These symptoms followed the closure of the fistula which occurred ninety-six hours before she came to the hospital. Her moribund condition prohibited surgical interference. At the autopsy, the typical picture of an acute pancreatitis was found, with cigarette-ash like flecks over the omental fat, free fluid of hemorrhagic character in the peritoneal cavity, and an hemorrhagic infiltration of the pancreas. Upon opening the duodenum a biliary calculus measuring 1.5 cm. in its longest diameter was found in the ampulla of Vater, and both biliary and pancreatic ducts proximal to the calculus were dilated.

The etiological significance of a calculus in this locality has often been commented upon, and it is given a prominent place in the surgical presentation of acute and chronic pancreatitis. Nevertheless, the discovery of the calculus is apparently rare in the experience of the surgeon, and its presentation at the time of autopsy is even less often observed.

Discussion.

DR. MOSCHCOWITZ. This seems to me another instance of the remarkable power of the human body to accommodate itself to maldevelopments. The cirrhosis of the liver is especially interesting, particularly in regard to the pathogenesis.

DR. LARKIN. I am interested in the portion of the liver found in the chest, the so-called hob-nailed part of the liver, which is bound to the other portions by rather thin bands which are evidently fibrous connective tissue, the vascular supply being still preserved. It is evidently a sequestrated part of the liver, which is still the greater functioning part of the organ. The thoracic portion, which has been rather reduplicated and pressed upon itself, has undergone the changes which are due to pressure; reversion to the ordinary fetal type has been more prominently represented in the so-called hob-nailed portion. It shows wonderful adaptation, and that nature is often very kind to us in the unusual mechanical displacements to which congenital conditions may lead. Congenital diaphragmatic hernias in which the abdominal viscera are displaced through different parts of the thorax are not so unusual. Those of us who have the opportunity of doing autopsies on fetuses often see them. The age of the individual and the wonderful accommodation he has shown are rather remarkable.

Dr. Moschcowitz: Last year I saw a case which was diagnosed as congenital diaphragmatic hernia. *X*-ray showed that the stomach was entirely inside of his chest. The hernia caused no discomfort, and the patient came to the hospital for another condition entirely.

AN UNUSUAL CASE OF SARCOMA OF THE STOMACH

GUSTAV A. PAGENSTECHER, M.D.

(*From the Pathological Laboratory of the Lenox Hill Hospital*)

Malignant connective tissue tumors of the stomach are not of frequent occurrence as compared with the high degree of frequency with which malignant epithelial tumors of this viscus are encountered. As is well known they present usually more or less well defined, lobulated growths, situated generally on the anterior wall of the stomach, and frequently, though not invariably, give rise to but few of the usual symptoms of a gastric neoplasm, chiefly because they but seldom obstruct the orifices of the organ.

The specimen presented here was removed postmortem from a female forty-three years old whose complaint upon admission to the hospital was weakness, pain in her abdomen and a mass in the left hypochondrium which had grown rapidly for one month. Physical examination showed a large mass, the general characteristics of which are shown in the specimen. Gastric analysis showed no free acid and a low total of 8 without occult blood. An exploratory laparotomy showed what was thought to be a retroperitoneal mass which was inoperable. Death occurred twelve days after operation. The autopsy showed as a chief pathological condition a large, more or less globular, tumor whose weight was eleven pounds. This tumor arose on the anterior wall of the stomach, the viscus having assumed the vertical position. In its growth the tumor had invaded and pushed itself between the two folds of the mesocolon transversely so that at operation it appeared as a retroperitoneal mass. Section through the stomach showed a large circinate ulcer without raised edges except for about one third of its circumference. This ulcer, situated 3.5 cm. from the pylorus, measured 7.5 cm. in its greatest diameter. There was no obstruction to either of the orifices of the stomach. Gross metastasis was not demonstrable, as is the case in 60 per cent. of these cases according to the investigations of Clendenning.

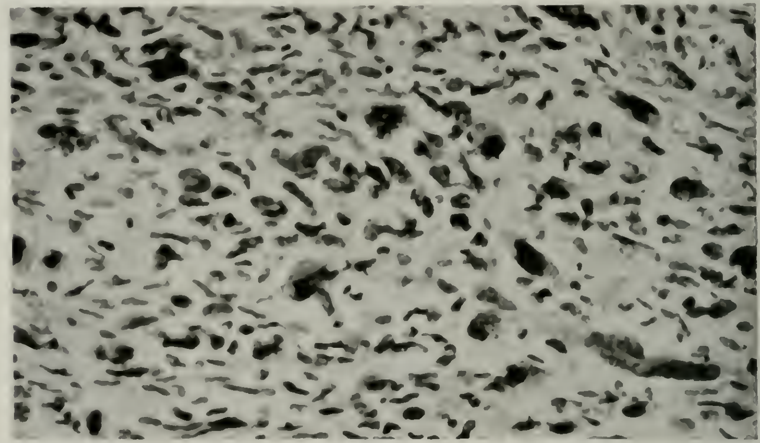


Fig. 1. Myosarcoma of stomach.

Histological examination showed the tumor to be composed of small spindle cells supported by delicate strands of connective tissue (Fig. 1). In some areas the neoplastic cells are arranged in spoke-fashion about very thin-walled blood vessels, suggestive of a perithelial sarcoma. Mitotic figures are not in evidence. There are numerous blood vessel tumor emboli and the growth is invading the surrounding tissues.

Discussion:

Dr. Ewing: I think the diagnosis in this case can be accepted as a myosarcoma, because the cells are spindle, large and small, with a very rich admixture of giant cells. The picture is rather characteristic of the myogenic sarcomas. I believe that this conclusion would be borne out by employing the stains used to demonstrate the character of the cells of a myogenic sarcoma. Eosin would probably show that the cells are distinctly eosinophilic, and Van Gieson's stain would show a certain specificity of the cytoplasm of the cells. The gross anatomy is also satisfactory for this diagnosis.

Dr. Larkin: I rather agree with the hasty microscopical diagnosis which has been made on this specimen, though at first from a rather cursory examination I was rather doubtful because of the tremendously large size of the tumor which is supposedly arising from the stomach wall. Now I am just about as much convinced as Dr. Ewing. But I would like to see a detailed study of the histology using different stains to establish the histological diagnosis of this tumor distinctly. Myogenic sarcomas are tumors of the stomach arising from the muscle. As far as I remember, this one is of unusually large size, and I think a more detailed study will have to be made to establish its direct pathological connection with the diagnosis which has been offered here to-night as a primary tumor of the stomach.

Dr. Pagenstecher: The clinical picture was rather clouded by the fact that this enormous tumor had grown in such a short time. It was only noticed about a month previous to admission, and a month and a half later the patient died. It grew very rapidly and gave no signs of pathological involvement. Pathologically, I think the tumor is a sarcoma arising in the muscular wall of the stomach, but the clinical picture is very confusing.

THREE UNUSUAL CONNECTIVE TISSUE TUMORS OF THE BREAST

ELISE L'ESPERANCE, M.D.

The comparative rarity of malignant connective tissue tumors of the breast, their peculiar histology, their bizarre gross appearance and doubtful histogenesis seems to justify the presentation here to-night of the following three cases.

Case I. The first case was on the service of Dr. Hartwell of Bellevue Hospital and the clinical history is as follows:

The patient, 39 years old, first noticed some small lumps in right breast about four years ago. They slowly increased in size and became fairly noticeable about one year ago. Since then the tumor increased to about ten times the original size. Three weeks previous to admission in hospital the patient suffered excruciating pain in breast and axilla and discomfort from rapidly increasing size of tumor (Fig. 1).

Gross examination reveals a large oval tumor of the right breast, lobulated and cystic in contour, measuring 30 inches in circumference, 12 inches in transverse diameter, and 15 inches in long diameter. The skin is not ulcerated or adherent and except for a cyanotic discoloration over the large nodules does not appear involved. The nipple is not retracted but shows a raised edematous area surrounding it. There is no lymphatic involvement.

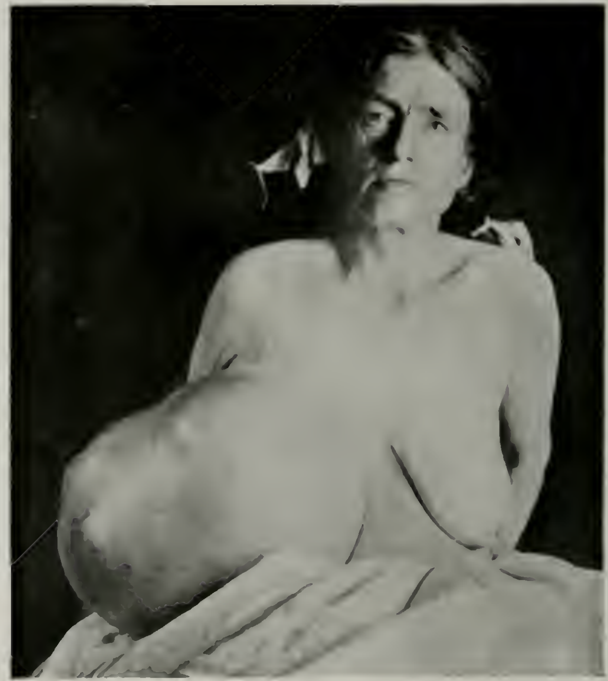


FIG. 1. Showing enormous size of tumor in Case 1.

The left breast shows chronic cystic mastitis, but no neoplasm.

On cross section the tumor reveals firm translucent areas with many small cysts filled with gelatinous material and a large well-circumscribed hemorrhagic and necrotic portion, which appears surrounded by a definite firm wall suggesting a hemorrhage into a large cyst.

Microscopical section shows a cellular large spindle cell sarcoma with edema and hemorrhage. The remaining areas of breast tissue are transformed into acellular hyaline tissue with a few isolated alveoli and ducts. These are associated with many large dilated blood vessels and multiple hemorrhages.

Case II. This case occurred at the Memorial Hospital on the service of Dr. Strobell.

The patient, 43 years old, noticed a small tumor in the left breast nine minthe ago, which grew rapidly. The family history was negative.

Gross examination reveals several large and small indurated and irregular masses, in the lower half of right breast and soft swelling in right supra-clavicular region. The breast and tumor measure 21 × 18 cm. deep. There is a fungating mass with central excavations protruding from an opening in the skin 7 cm. in diameter just below the nipple. This opening leads into a large cavity discharging necrotic and putrefying tumor tissue. On cross section there is found a well-circumscribed, encapsulated, soft, translucent tumor, centrally excavated, 18 cm. in diameter. An additional tumor of characteristic papillary fibro-adenomatous type lies just beneath the main tumor. This measures 6 cm. The small remaining portion of the breast shows diffuse fibrosis.

Microscopical examination shows the main tumor is a cellular edematous spindle cell sarcoma arising from fibro-adenoma of intra-canalicular type. The smaller outlying tumor is an intra-canalicular and papillary fibroma. The remaining breast tissue shows fibrosis.

Case III. The patient, aged 54 years, noticed a small lump in breast twenty-five years ago, which did not increase in size until about two years ago.

Gross examination shows nodular, irregular, circumscribed tumor mass involving the greater part of the right breast. There is skin involvement and no enlargement of regional lymph nodes. On cross section one finds firm dense nodules in whorl arrangement occupying the greater part of the tumor, with a few small hemorrhagic areas. In the lower outer portion of the breast there is a well-circumscribed hemorrhage 1 × 1 inch with well-defined wall.

Microscopically the main mass of the tumor consists of small spindle cells arranged in whorls and interlaced bands, typical of a fibro-sarcoma. The remaining breast tissue at the margin of the tumor shows extreme fibrosis with hyaline degeneration which surrounds the ducts and atrophied alveoli.

In a study of these cases several facts demand particular attention: First, the relatively long quiescence of small nodules in the breast. (Gross reports a case in which a nodule remained of the same size for 36 years and at the age of 63 began rapidly to grow, doubling its size in one year. Robin reported a similar case.) Second, the sudden and extremely rapid growth at a later period. The age incidence of spindle cell sarcomas varies, usually, from 39 to 49 years. The increase in size is not only more rapid than in other tumors, but varies widely and is usually influenced by their structure, the presence or absence of cysts or associated hemorrhage. This is well shown in the first case reported where the enormous size was in great part due to the large hemorrhages into cysts. Third, ulceration of the overlying tissues is rather common, occurring in about 18 per cent. of the reported cases. Ulceration occurred in the second case reported here and showed the characteristic type of deep fungating ulcers. The histogenesis is the point of especial interest in these neoplasms and opens a wide field for speculation. Undoubtedly in the majority of cases a previous intra-canalicular fibroma proves the starting point of these neoplasms, as is well shown in the second case from the Memorial Hospital. However, Case No. 1 shows no evidence of a previous benign neoplasm and was undoubtedly preceded by an extensive diffuse fibrosis of the breast, as evidenced in the remaining marked diffuse fibrous mastitis which is observed in the other portions of the mammary gland and was also noted in the opposite breast. The short duration in this case is against the theory of a preceding benign fibroma. It is not unreasonable to suppose that a diffuse fibrosis may precede this type of cystic sarcoma. In the third case we have neither a fibroma nor marked extensive fibrosis to suggest a point of origin. The histological structure with the arrangement of spindle cells in whorls and strands so often encountered in fibro-sarcomas of neurogenic origin leads one to suspect an origin from nerve sheaths of the same histological character and histogenesis as the neurogenic sarcomata of other regions.

Discussion:

Dr. Ewing: We have removed early this week at the Memorial Hospital another specimen of sarcoma of the breast, about two thirds as large as the largest specimen here. It occurred in a woman sixty-five years of age. It had existed for several years, but had grown rapidly during the past six months. The patient was decidedly emaciated and cachectic through absorption from several softened necrotic areas in the huge tumor mass. The skin was intact, and the tumor well encapsulated.

VOLUME XIX, 1919

INDEX

A

Agglutinins and hemolysins, normal, of human blood, is there a parallelism between? Reuben Ottenberg and Frances Krasnow 83

Anemia, Von Jaksch's, a case of, occurring in a child five and one half months old. William C. Thro 6

Appendix, lymphosarcoma of, in a child. George L. Rohdenburg 2

Applebaum, E., and Symmers, Douglas. Vaquez's disease.. 10

B

Bactericidal substances, nonspecific, the production of, by means of staphylococcus and streptococcus vaccines in vivo and in vitro. R. Ottenberg and K. Wallach 55

Baehr, George. Periarteritis nodosa 131

Barach, Alvan L. Report of a case of cyst of the testicle in a dog 38

Bernhard, Adolph, Rohdenburg, G. L., and Krehbiel, Otto. Sugar tolerance in cancer.... 54

B. influenzæ, relationship of, to clinical influenza. F. M. Huntoon and S. Hannum...... 22

Bone formation, extensive, in thyroid. H. Willy Meyer... 70

Breast, a case of carcinosarcoma of. A. O. Wilensky........ 113

Breast, a case of giant celled sarcoma of. D. S. D. Jessup. 117

Breast, three unusual connective tissue tumors of. Elise L'Esperance 165

C

Cancer, sugar tolerance in. G. L. Rohdenburg, Adolph Bernhard and Otto Krehbiel.... 54

Carcinoma, diffuse, of stomach. L. C. Knox 143

Carcinoma, embryonal, of ovary. L. W. Strong 71

Carcinoma of ovary. Emil Schwartz 72

Carcinoma, primary, of fallopian tube. G. L. Rohdenburg..... 2

Carcinoma of rectum in a boy of sixteen. L. W. Strong...... 71

Carcinoma of tube. Emil Schwartz 72

Carcinoma of the uterus in a mouse. William H. Woglom 60

Carcino-sarcoma of the breast, a case of. A. O. Wilensky.... 113

Cecitis, chronic, of unknown origin, a case of. A. O. Wilensky 51

Chorioepithelioma of fallopian tube. L. W. Strong......... 71

Congenital bilateral stricture of the ureter. Isidor Mufson.. 66

Cyst of the testicle in a dog, report of a case. Alvan L. Barach 38

Cysticercus of the fourth ventricle. Leo Loewe 127

D

Danchakoff, Vera. Digestive capacity of splenic adult mesenchyme as factor in tumor production 136
Diaphragmatic hernia, an unusual case of. H. F. Pohlman.... 160

E

Eosinophilic (polymorphonuclear) leukemia. Louis G. Shapiro 73
Ewing, James. A case of thymoma 156
Ewing, James. Pulmonary lesions of influenza pneumonia, and a method of museum preparation 15

F

Fallopian tube, chorioepithelioma of. L. W. Strong........... 71
Fallopian tube, primary carcinoma of. G. L. Rohdenburg 2
Fibroadenoma of the umbilicus. G. L. Rohdenburg 2

H

Hannum, S., and Huntoon, F. M. The relationship of *B. influenzæ* to clinical influenza.. 22
Hemolysins and agglutinins, normal, of human blood, is there a parallelism between? Reuben Ottenberg and Frances Krasnow 83
Hernia, diaphragmatic, an unusual case of. H. F. Pohlman 160
Huntoon, F. M., and Hannum, S. The relationship of *B. influenzæ* to clinical influenza...... 22

I

Influenza, clinical, relationship of to *B. influenzæ*. F. M. Huntoon and S. Hannum....... 22
Influenza pneumonia, pulmonary lesions of, and a method of museum preparation. James Ewing 15
Intestinal tuberculosis, primary. Max Palinsky 149

J

Jessup, D. S. D. A case of giant celled sarcoma of the breast 117

K

Klingenstein, P. A. A case of thymoma 151
Knox, L. C. Diffuse carcinoma of stomach 143
Knox, L. C. Two cases of myxo-lipo-sarcoma, retroperitoneal 90
Krasnow, Frances and Ottenberg, Reuben. Is there a parallelism between normal agglutinins and hemolysins of human blood? 83
Kreihbiel, Otto, Rohdenburg, G. L. and Bernhard, Adolph. Sugar tolerance in cancer.... 54

L

L'Esperance, Elise. Three unusual connective tissue tumors of the breast 165
Leukemia, eosinophilic (polymorphonuclear). Louis G. Shapiro 73
Levy, I. J. A pathological classification of nephritis based upon clinical findings 121
Loewe, Leo. Cysticercus of the fourth ventricle 127
Lymphosarcoma of the appendix in a child. G. L. Rohdenburg 2

M

Melanocarcinoma, two unusual cases of. H. A. Murray..... 28

Mesenchyme, splenic adult, digestive capacity of, as factor in tumor destruction. Vera Danchakoff 136
Meyer, H. Willy. Extensive bone formation in the thyroid 70
Mufson, Isidor. Congenital bilateral stricture of the ureter.. 66
Murray, H. A. Two unusual cases of melanocarcinoma 28
Myositis ossificans. G. L. Rohdenburg 2
Myxo-lipo-sarcoma, retroperitoneal, two cases of. L. C. Knox 90

N

Nephritis, a pathological classification of, based upon clinical findings. I. J. Levy.......... 121

O

Ottenberg, Reuben, and Krasnow, Frances. Is there a parallelism between normal agglutinins and hemolysins of human blood? 83
Ottenberg, Reuben, and Wallach, K. The production of nonspecific bactericidal substances by means of staphylococcus and streptococcus vaccines in vivo and in vitro 55
Ovary, carcinoma of. Emil Schwartz 72
Ovary, embryonal carcinoma of. L. W. Strong 71

P

Pagenstecher, Gustav A. An unusual case of sarcoma of the stomach 163
Palinsky, Max. Primary intestinal tuberculosis 149
Pancreatitis, acute, a case of, due to calculus in ampulla of Vater. H. F. Pohlman 160
Pappenheimer, Alwin M. The pathology of the poisonous gases used in the war 97
Periarteritis nodosa. George Baehr 131
Pohlman, H. F. An unusual case of diaphragmatic hernia.. 160
Pohlman, H. F. A case of acute pancreatitis due to calculus in ampulla of Vater...... 160
Production of nonspecific bactericidal substances by means of staphylococcus and streptococcus vaccines in vivo and in vitro. Reuben Ottenberg and K. Wallach 55
Pulmonary lesions of influenza pneumonia, and a method of museum preparation. James Ewing 15

R

Rectum, carcinoma of, in a boy of sixteen. L. W. Strong.... 71
Rohdenburg, G. L. Fibroadenoma of the umbilicus....... 2
Rohdenburg, G. L., Bernhard, Adolph, and Krehbiel, Otto. Sugar tolerance in cancer.... 54
Rohdenburg, G. L. Lymphosarcoma of the appendix in a child 2
Rohdenburg, G. L. Myositis ossificans 2
Rohdenburg, G. L. Primary carcinoma of the Fallopian tube.. 2

S

Sarcoma, giant celled, of the breast, two cases of. D. S. D. Jessup 117
Sarcoma of the stomach, an unusual case of. Gustav A. Pagenstecher 163
Schwartz, Emil. Carcinoma of tube 72

Schwartz, Emil. Carcinoma of ovary ... 72

Shapiro, Louis G. Eosinophilic (polymorphonuclear) leukemia 73

Splenic adult mesenchyme, digestive capacity of, as factor in tumor destruction. Vera Danchakoff ... 136

Stomach, an unusual case of sarcoma of the. Gustav A. Pagenstecher ... 163

Stomach, diffuse carcinoma of. L. C. Knox ... 143

Stricture, congenital, bilateral, of ureter. Isidor Mufson ... 66

Strong, L. W. Chorioepithelioma of Fallopian tube ... 71

Strong, L. W. Embryonal carcinoma of ovary ... 71

Strong, L. W. Carcinoma of rectum in boy of sixteen ... 71

Sugar tolerance in cancer. G. L. Rohdenburg, Adolph Bernhard, and Otto Krehbiel ... 54

Symmers, Douglas, and Applebaum, E. Vaquez's disease .. 10

T

Testicle, cyst of the, report of a case in a dog. Alvan L. Barach ... 38

Thro, William C. A case of von Jaksch's anemia occurring in a child five and one half months old ... 6

Thymoma, a case of. P. Klingenstein ... 151

Thymoma, a case of. James Ewing ... 156

Thyroid, extensive bone formation in. H. Willy Meyer ... 70

Tube, carcinoma of. Emil Schwartz ... 72

Tube, Fallopian, chorioepithelioma of. L. W. Strong ... 71

Tube, Fallopian, primary carcinoma of. G. L. Rohdenburg. 2

Tuberculosis, primary intestinal. Max Palinsky ... 149

Tumor destruction, digestive capacity of splenic adult mesenchyme as factor in. Vera Danchakoff ... 136

Tumors of the breast, three unusual connective tissue. Elise L'Esperance ... 165

U

Umbilicus, fibroadenoma of the. G. L. Rohdenburg ... 2

Ureter, congenital bilateral stricture of. Isidor Mufson ... 66

Uterus, carcinoma of, in a mouse. William H. Woglom 60

V

Vaquez's disease. Douglas Symmers and E. Applebaum ... 10

Ventricle, fourth, cysticercus of. Leo Loewe ... 127

Von Jaksch's anemia, a case of, occurring in a child five and one half months old. William C. Thro ... 6

W

Wallach, K., and Ottenberg, Reuben. The production of nonspecific bactericidal substances by means of staphylococcus and streptococcus vaccines in vivo and in vitro ... 55

Wilensky, A. O. A case of carcino-sarcoma of the breast ... 113

Wilensky, A. O. A case of chronic cecitis of unknown origin ... 51

Woglom, William H. Carcinoma of the uterus in a mouse 60

PROCEEDINGS

OF THE

NEW YORK PATHOLOGICAL SOCIETY

NEW SERIES, VOLUME XX
1920

Organized in 1844 Incorporated in 1886

NEW YORK
1920

PRESS OF
THE NEW ERA PRINTING COMPANY
LANCASTER, PA.

/

Proceedings
of the
New York Pathological Society

New Series, Vol. XX JANUARY–MAY, 1920 Nos. 1-5

CONTENTS

PAGE

The Glycemic Reaction, Its Clinical Significance, and its Relation to Immunity. *George L. Rohdenburg, M.D.* 1

A Case of Right-sided Endocarditis (*Streptococcus viridans*). *Frederich H. Dieterich, M.D.* 5

A Case of Gastroileostomy Surviving Operation Five Years. *Andrew E. Eggstein, M.D., and Herman L. Frosch* 9

Experimental Studies in Encephalitis Lethargica. *Leo Loewe, M.D., and Israel Strauss, M.D.* 18

Aneurysm of the Hepatic and Gastroduodenal Arteries, with Rupture of the Aneurysm into the Duodenum. *Henry R. Muller, M.D.* 46

A Case of Sarcoma of the Lung. *A. V. St. George, M.D.* 48

A Case of Acute Yellow Atrophy, with Compensatory Changes in the Liver. *Eli Moschcowitz, M.D.* 54

Pathological Findings in Seventeen Cases of Pneumonia During the Influenza Epidemic of January–February, 1920. *Henry E. Meleney, M.D., and Alwin M. Pappenheimer, M.D.* 56

The Pathology of Experimental Pneumonia. *Russell L. Cecil, M.D.* 62

Carcinoma of the Bronchus with Thrombosis of the Superior Vena Cava. *Ralph G. Stillman, M.D.* 66

Localized Changes in the Heart Muscle as Determined to be in the Right Bundle Branch by the Electrocardiograph. *Louis Faugeres Bishop, M.D.* 70

A Simpler Way of Preparing Colloidal Gold Solution. *Max Lederer, M.D.* 87

Precipitin Formation in a Patient with Serum Disease showing Immediate and Accelerated Reactions. *George M. Mackenzie, M.D.* 91

Dr. James W. Jobling, *President.*

THE GLYCEMIC REACTION, ITS CLINICAL SIGNIFICANCE, AND ITS RELATION TO IMMUNITY

G. L. ROHDENBURG, M.D.

(From the Pathological Laboratories of the Lincoln and Lenox Hill Hospitals, New York)

This article has been published in *The American Journal of Medical Sciences*, 1920, clix, 577, 853, and *Jour. Cancer Research*, 1920, Oct.

Discussion.

Dr. Geyelin: Dr. Rohdenburg presented such a vast mass of experimental detail that I find myself a little confused in trying to grasp it at all in the time given. There was one thing about the blood sugar curves in the experimental animals that I think is of some importance in interpreting the results, and that is, under what conditions of nutrition were the animals at the time the experiments were carried out? There is another point that I do not quite understand—the point Dr. Rohdenburg made about the significance of the types of the curves in the various clinical conditions. As I understood it, he said there was a distinct curve which had a definite relationship to immunity, and I do not see just what connection that had with the type of diseases he mentioned. I think the whole matter is an extremely interesting problem, and I agree with Dr. Rohdenburg that there is probably a great deal about it which is still obscure.

Dr. Mosenthal: I feel somewhat as Dr. Geyelin does—that I have been presented with a mass of details which are difficult to grasp in a short time, but there are a few facts which seem worthy of consideration, because this question is of such very great importance.

In the first place, many of us depend largely on the type of blood sugar curve in making a diagnosis of incipient diabetes. The method that has been worked out by Hamman, Williams, Janney and others makes it evident that this is a very significant phenomenon. The normal blood sugar curve, after the ingestion of 100 grams of glucose, is, within certain limits, a perfectly definite one. A normal blood sugar curve will exclude the diagnosis of diabetes. It must be recognized, however, that a positive one may occur in diseases other than diabetes; such abnormal curves have been demonstrated in nephritis, hypertension, thrombo-angiitis obliterans, and undoubtedly they will be found in other conditions. The method of obtaining the blood sugar curve in the present communication will fail to demonstrate the maximal blood sugar in most instances, as the highest blood sugar level in normal individuals is reached before forty minutes have passed after the ingestion of glucose. Hence the observations in regard to the renal threshold for glucose are only approximate. It is certainly true, as Dr. Rohdenburg has said, that the renal threshold is raised in many cases in which no renal disease or insufficiency can be demonstrated. If this problem is more thoroughly worked up, it may be of very great aid in the treatment of diabetes mellitus.

The type III reaction in this paper I believe really should be regarded as an extremely rapid type of normal curve. It is perfectly conceivable that within forty minutes the blood sugar may have risen as the result of glucose ingestion, and again dropped to the control or sub-control within this time.

The question of the relation of immunity and blood sugar is one of the most pressing problems in guiding the treatment of cases of diabetes mellitus that is confronting us. It is well established that the blood sugar of almost all diabetics may be reduced to normal, but is it advisable to do so? Should we sacrifice body weight and physical efficiency by the administration of low diets in order to bring the blood sugar to a normal level? If the immune reactions are rendered more efficient by reducing the blood sugar to normal a very definite answer to our question has been obtained. Whether the increased resistance reduced the blood sugar in these experiments, or whether the lowered blood sugar produced the increased resistance, is an open question. My own impression from the data presented to-night was that probably the increased resistance was responsible for the diminished blood sugar and not vice versa. This, if correct, would furnish the practical information that it is not worth while to diminish the blood sugar in order to increase the resistance.

I think it is worthy of note that usually those cases which have an unusually high blood sugar will have a tendency to have less of a rise in their blood sugar curve after the administration of glucose than those patients who have an initial low blood sugar. From that point of view it would seem that a high sugar level in the blood makes for a more efficient digestion of carbohydrate.

In closing I wish to express my admiration of the great amount of work so accurately and intelligently carried out by Dr. Rohdenburg and his associates.

Dr. Kahn: The two previous speakers have the advantage of me in announcing the fact that the subject matter was too detailed and long to grasp by watching the slides. In fact, before I came to this meeting the program seemed to be rather mysterious. I saw no relation between glycemia and immunity. As to the production of glycosuria in animals by means of various endocrine substances which were injected, it is a known fact that the diet of animals previous to the administration of the endocrine substance influences the appearance of hyperglycemia and glycosuria, especially the presence or absence of calcium has a very marked effect on the production of glycemia. That is, if an animal has a high calcium intake previous to the administration of adrenalin or the xanthine bodies, etc., it is almost impossible to induce a hyperglycemia. If Dr. Rohdenburg would give us a résumé of the relations of hyperglycemia or hypoglycemia to immunity I would be very glad.

Dr. Stevens: I think this paper has opened up some very interesting questions. It seems to me especially important if you consider that some of the reactions, hypo- and hyperglycemia especially, might be established during the process of immunity which can be likened to some of the other changes which take place in a patient during the time that he is having fever. If you take a case of pneumonia while immunity is being established, there is a great retention of salt. We know that this retained salt is distributed quite generally, and it seems to me that this shows that during the time the patient is developing immunity the production of the immune substances changes the permeability of the cells throughout the body, and that changes the relationship of the salts; that would come in very well with glycemic changes at the same time. It seems to me that perhaps immunity in itself results in various changes in permeability that are produced by proteins. I know that in working with hemolysins the action of various sugars reduces the action of the hemolysins, especially if the hemolysins are those of the streptococcus, so it is possible that there is a great deal in this relation of the sugar to the permeability of the cell.

Dr. Rohdenburg: In answer to Dr. Geyelin's question in regard to the nutrition of the animals, they were starved for twelve hours previous to beginning the experiments. For several weeks before the test they received the usual laboratory diet which consists practically entirely of carbohydrates—bread, carrots, and once in four days, meat.

The time periods chosen and the curves plotted on these time periods were more or less arbitrary, and we were more or less driven to adapting them. If we compare "typical" diabetic curves as given in the literature, we find that there is no such thing. This confusion arises because some authors take blood specimens every fifteen minutes, and others continue their observations up to six hours. In brief, there is no regularity. We have not viewed the problem as a study in metabolism, but we have taken it purely as a functional test of endocrine activity.

As far as the relation of immunity to hyperglycemia is concerned, we cannot state whether the hyperglycemia which follows the repeated injection of a protein is the thing which produces the immunity, or whether it is simply a result of the general chemical process that occurs during the development of immune bodies. Whether hyperglycemia so induced is due to the increase in the temperature known to follow the injection of proteins, or whether it is due to the breaking up of the protein molecule, is also almost impossible to state. The interesting point is that the two phenomena run to some degree hand in hand. I do not believe that we can establish a direct relationship, but can only say that the two occur concurrently.

A CASE OF RIGHT-SIDED ENDOCARDITIS (STREPTOCOCCUS VIRIDANS)

FREDERICK H. DIETERICH, M.D.

(From the Pathological Laboratory, Presbyterian Hospital, New York City)

The family history of this patient is negative. The past history is important in that it gives no history of rheumatism, and that the patient was rejected from the army twenty years ago for "heart trouble." He had gonorrhœa and soft chancre fifteen years ago, and sore throats about once every two years.

Present Illness: Up to one year ago this patient was perfectly well. Then trouble with teeth commenced for which he had to go to the dentist's. Several teeth were capped. He was then well again up to about eight months ago, since which time he has been ailing. The illness started with pain in the sacral region. This was followed by a pain in the splenic region, more marked on deep breathing, and accompanied by nosebleed. Two weeks later, he had a similar pain in the right side. Five months ago, he noticed that he was losing color. One month after this—in other words about four months ago—pain developed around the heart, and after persisting about a week disappeared, only to re-appear on the right side for a similar length of time. With this, pains and swelling developed in his ankles and then in the knees of both lower extremities, with fever, which he thinks has lasted ever since. In point of fact, all the symptoms which developed then have persisted during these four months until admission to the hospital—such as dyspnœa, frequency of urination, œdema of lower extremities and hemorrhagic spots. For the last month stools have been very dark.

Physical Examination: The patient is a weak, anæmic male. Over the entire body, more marked over the lower extremities, are numerous large and small petechiae. Toes and fingers are clubbed. Lungs show dullness, diminished fremitus and crackling râles over the right lower lobe. Heart is enlarged, with systolic thrill at apex, and systolic murmur over the entire precordium.

Blood Pressure: 147/48. *Blood Wassermann:* Negative. *Group:* II.

Blood Culture: Streptococcus viridans. 75 colonies per c.c.

Blood Count: W. B. C. 19,850. Polys. 78 per cent. Lymphos. 22 per cent.
R. B. C. 1,500,000–2,500,000. Hgb. 45–35 per cent.

Blood Urea: 0.25 gm. per liter.

Stool: Guaiac negative. No ova or parasites. Marked increase in urobilinogen and urobilin.

X-ray of Hands: Shows slight destruction and thickening of periosteum of the first phalanges of the 2d, 3d, 4th and 5th fingers.

Spinal Fluid: Clear, under pressure; culture negative.

Urine: Sp. Gr. 1010–12. Trace of albumin, with hyaline casts.

Autopsy: Aside from marked congestion of both *lungs* postero-inferiorly and several rather dense adhesions on both sides with a small amount of pleural fluid in the right chest, the thorax shows no abnormalities except in the specimen I have to present this evening. The *liver* shows a cloudy swelling and the *kidneys* a chronic nephritis.

Heart weighs 375 grams. The pericardium is smooth and glistening throughout. The muscle wall of the left heart at its thickest portion measures 2 cm. It is of good color, and shows no myocardial scars. The endocardium, aside from a few atheromatous plaques at the base of the mitral valve, also shows no changes. The anterior cusp of the aortic valve on its ventricular surface shows a small firm vegetation in the region of the corpus arantii. Aside from a marked hypertrophy of the papillary muscles of this side, there are no other visible changes to be noted in the left heart. The right heart shows a slight dilatation of the right auricle. The foramen ovale is completely obliterated. The thickest portion of the right ventricular wall measures 1 cm. The tricuspid valve, at the line of attachment, is soft and pliable and free of any atheromatous plaques. As its free border

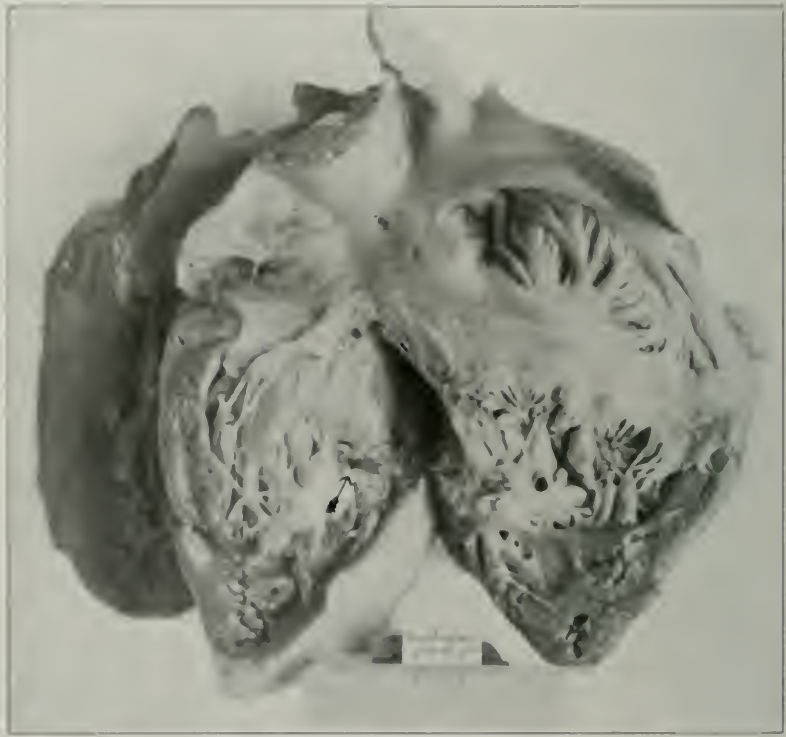


FIG. 1. Right heart. Vegetations on chordæ tendinæ and cusps of tricuspid valve.

is approached, however, it becomes thicker and has numerous warty vegetations on both surfaces. (Fig. 1.) These vegetations are in some places firm and pearly white, and in others pinkish and rather friable, their size varying from 0.5 to 7 mm. The papillary muscles in the upper portion of the ventricle stand out quite prominently and show no fibrosis at all at their apices, where they are attached to the chordæ tendinæ of the posterior, or septal, cusp of the valve. This cusp also contains very few vegetations. The chordæ tendinæ of the other cusps are markedly thickened and matted together. This is especially true of those attached to the right or marginal cusp. Here the chordæ tendinæ arise from the apices of several papillary muscles, fused at their tips into a sclerotic mass of tissue. Between this mass of matted together chordæ tendinæ and the ventricular wall is found a pinkish laminated vegetation, measuring about 1 cm in thickness and 2 cm. in length. This overlies a perforation in the interventricular muscular septum, about 5 cm. from the apex of the heart and 3 cm. below the anterior cusp of the aortic semilunar valve,—in other words the perforation lies in the muscular interventricular septum. At its margins, the openings into this perforation on both sides of the heart are surrounded by very small pinkish vegetations, rather warty in character, upon a pale sclerotic rim. The en-

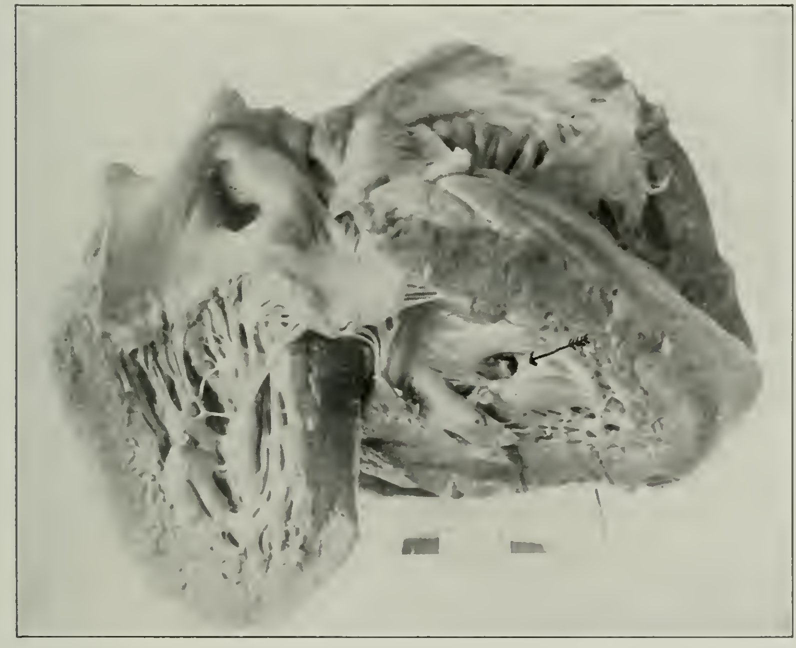


Fig. 2. Left heart. Defect in interventricular septum found between two adjacent papillary muscles.

trance into this passage on the left side of the heart is oval, 2.5 x 1 mm. in diameter, and found at the base of a funnel-shaped depression 1 cm. deep, between two adjacent, thick, papillary muscles (Fig. 2.) On the right side, the opening is round and also lies in a shallower depression between two papillary muscles, and measures 2 mm. in diameter. No ulceration of the endocardium is found. The pulmonary valves are soft and pliable. Throughout the course of the coronary blood vessels, there are atheromatous patches, but no calcification can be noted. Post-mortem blood culture shows *streptococcus viridans.*

The measurements are as follows:

Pulmonary valve	7.5	cm. in circumference
Tricuspid valve	12	cm. in circumference
Mitral valve	10	cm. in circumference
Aortic valve	6.5	cm. in circumference
Left ventricle	13	mm. in thickness
Right ventricle	4	mm. in thickness

Discussion:

Dr. Baehr: This condition is undoubtedly a very rare one. I would like to ask whether the glomeruli were found as they characteristically are in this disease when it occurs on the left side. It is conceivable that in this instance the lung acted as a filter, which did not permit the passage of the minute bacterial emboli which are responsible for the characteristic glomeruli in the kidney. Were these looked for and were they found?

Dr. Norris: A perforation in that situation is an extraordinarily rare one. I think Dr. Wood showed years ago, in 1910 possibly, a specimen something like this. I have never seen an opening in this situation. Congenital defects of the heart, but hardly perforations in this location, without other congenital defects, are more or less frequent. The question arises is this a congenital perforation, or a healed perforation due to chronic *streptococcus viridans* infection? I make that only as a suggestion. I do not know if one can readily disprove or confirm this. It might be very difficult to come to a definite conclusion as to which opinion was correct, namely, whether the perforation had existed from birth, or if it was, as I suspect it may have been, a healed ulceration from previous attacks. Dr. Libman has shown that a great many of the *viridans* infections are very insidious, and run a more or less chronic course. I meant to ask if the patient had previously any cyanosis, but with the small size of the perforation one would not expect it to be present. It would be similar to the small patent foramen which is practically, physiologically speaking, always closed.

Dr. Moschcowitz: The lesion interested me because I presented before the Society some years ago a right-sided *Streptococcus viridans* infection, only it involved the pulmonary valve, instead of the tricuspid.

Dr. Dieterich: In regard to Dr. Baehr's question, I would say that we made a frozen section of the kidney, and did not find any of those lesions of the glomeruli described by Löhlein, but the paraffin sections have not come through yet, so I cannot say definitely whether they were present or not.[1]

Concerning Dr. Norris's suggestion, we thought of that ourselves, that it might be an ulceration through the interventricular septum, but bearing in mind that this man was well until about a year ago, and that twenty years ago he was rejected by the Army authorities because of his "heart trouble," we thought it was likely that at that time he had the signs of heart trouble due to a congenital defect, and that later on he developed this *streptococcus viridans* infection. There was no history of cyanosis.

A CASE OF GASTROILEOSTOMY SURVIVING OPERATION FIVE YEARS

ANDREW A. EGGSTEIN, M.D., AND HERMAN L. FROSCH

(*From the Department of Pathology, Presbyterian Hospital, New York*)

During the past year there came to autopsy at the Presbyterian Hospital a case of seemingly sufficient interest to justify its being reported. The interesting features were the anomalous type of surgery the patient received and the length of time the patient survived the operation. Many studies upon the metabolic and physiologic disturbances following extensive short circuiting of the small intestines have been recorded upon experimental animals, particularly dogs, but few human cases have been studied to corroborate the findings upon the experimental animals. In fact, we were unable to find a human case similar to this one reported in the literature.

Abstract of Clinical History.—The patient was a white man, 47 years of age, a clerk by occupation. He was admitted to the Presbyterian Hospital November 29, 1918, sixteen days before his death, complaining of a progressive loss of weight and strength for two years, associated with nocturia and excessive hunger and thirst. The loss of weight had been more marked for the last six weeks. The essential feature of his past history was a severe stomach trouble which began ten years previous to the present illness and which lasted five years. This was relieved by an operation for gastric ulcer. At the time of the operation he weighed seventy pounds. Following the operation the patient gained sixty pounds and felt practically normal for a period of two years. He regained his former strength, but a frequency in defecation began which persisted in spite of his sedentary habits. The stools were soft and pasty, and fluid at times. The bowel frequency was somewhat influenced by the diet. A high protein, or carbohydrate, diet had no noticeable influence upon the bowel movements, while a diet rich in fats invariably increased the frequency of defecation, and at times produced a severe enteritis which was only relieved by a radical change in the diet. Foods containing considerable admixture of insoluble material likewise produced a diarrhea. The patient became very susceptible to purgatives following the operation, a very mild purgative producing rapid and severe catharsis.

---

[1] Paraffin sections, made later, show a diffuse glomerular nephritis only.

The patient's family history revealed nephritis in the father, but otherwise it was irrelevant.

The illness which brought him to the hospital was a rapidly progressive loss of strength and weight. During the last two months he had lost the sixty pounds which he gained after the operation, weighing when admitted only seventy pounds.

Physical examination revealed an extremely emaciated man. The intercostal spaces were deeply sunken. The abdomen was scaphoid and the extremities very small. The patient's mentality was good. The lungs were hyper-resonant but no râles were heard. The heart was negative. Upon the median line of the abdomen above the umbilicus there was an old operative scar. The liver was not enlarged. No areas of tenderness were elicited in the abdomen. A soft irregular mass was found in the hypogastric and umbilical regions, just left of the median line.

Blood pressure was 120/60.

Blood urea, 0.3 gm. per liter.

Blood Count: Red blood cells 3,900,000. White blood cells 11,600. Hemoglobin 80 per cent. Neutrophiles 70 per cent. Lymphocytes 29 per cent. Eosinophiles 1 per cent.

Stool examinations were made six times; at no time was blood demonstrated.

Urine showed a specific gravity of 1.020, a faint trace of albumin, and no sugar. Microscopically at times a few hyaline, granular, fatty and waxy casts were found.

Stomach contents: One fasting expression yielded 10 c.c. of thick brownish fluid containing bacilli and undigested food but no blood. The free hydrochloric acid was 0. Total acidity 20. After an Ewald test meal, 200 c.c. fluid was recovered containing undigested food, many bacilli, free hydrochloric acid, 0. Total acidity 6.

X-ray of stomach eleven days before death showed a regular indentation on the lesser curvature, not associated with the peristaltic wave on the greater curvature which was interpreted to mean a probable gummatous infiltration, or spasm indicative of an old ulcer in the pylorus and gastro-enterostomy. (Figs. 1 and 2.)

Course of last illness was progressively downward, the patient becoming asthenic. Glucose infusions were given without effect. The blood count three days before death showed no change. The patient's temperature was normal until two days before death, when it increased to 101° C. The pulse rate was about 85 but increased to 140 just before death.

Clinical Diagnosis: Carcinoma of stomach.

Autopsy was performed three hours postmortem. The body was that of a white man 175 cm. long, weighing seventy pounds and showing enormous emaciation. The superficial mucous membranes were pale. The muscles were soft and prominent, due to the marked emaciation. The abdomen was

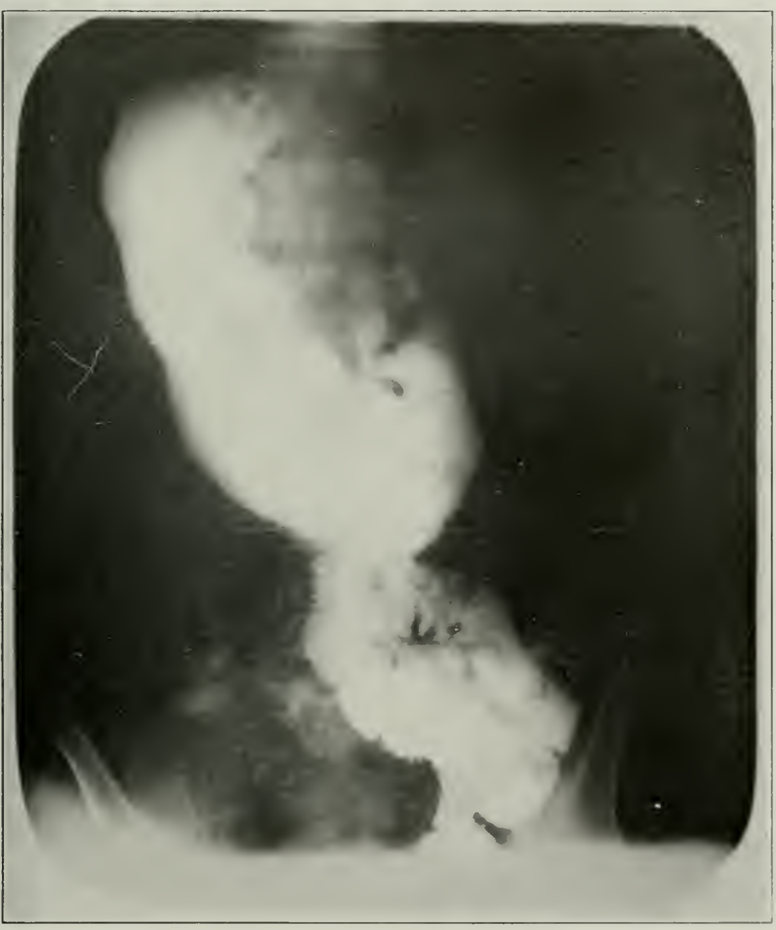


FIG. 1. X-Ray immediately after a bismuth meal. Erect posture. Showing rapid emptying of bismuth into lower ileum and cæcum. This also shows the marked constriction of the pylorus.

scaphoid. In the median line above the umbilicus there was an old scar 14 cm. long. Median incision revealed little subcutaneous fat and muscle of a bright brownish red color. The peritoneum was smooth. The omentum was adherent to the anterior abdominal wall at the site of the previous operation. The colon was dilated with gas and the transverse colon showed considerable

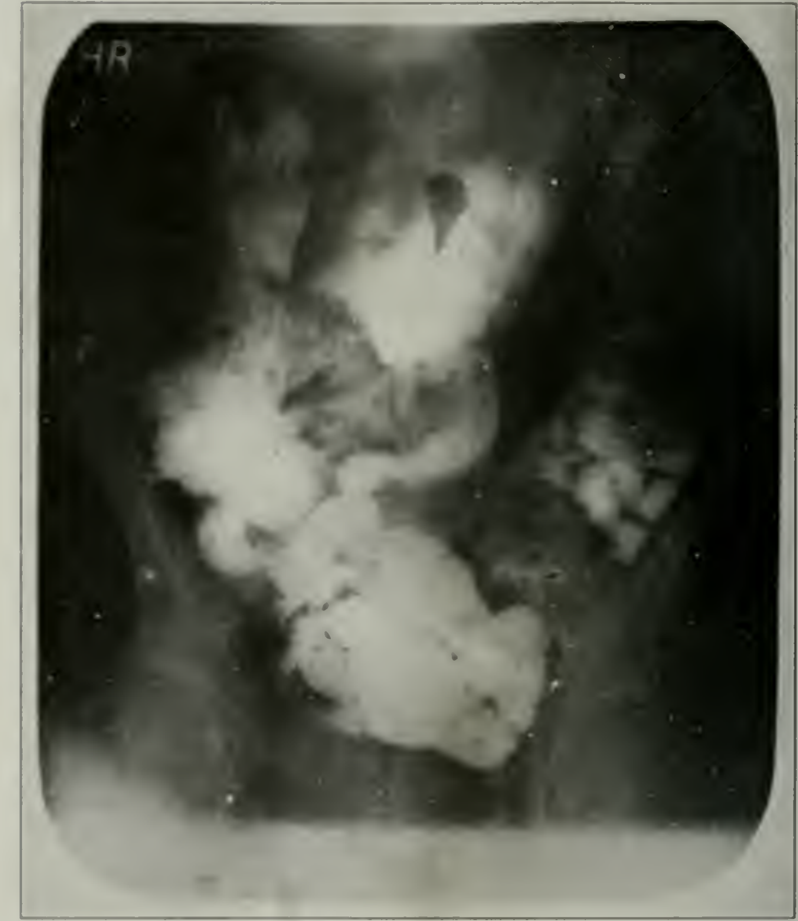


FIG. 2. X-Ray four hours after a bismuth meal, showing only a small amount of the bismuth in the stomach, while the colon and ascending colon contain a large amount. Note prolapse and size of cæcum.

ptosis. The stomach and small intestines were collapsed. The appendix was apparently normal. The spleen and liver were small. The mesenteric lymph glands were enlarged. Upon close examination the transverse mesocolon was rather short and the colon and stomach were situated very near together. The transverse mesocolon was penetrated by a loop of the ileum which was firmly attached to the greater curvature of the stomach. This loop of ileum was also adherent to the mesenteric border of the transverse colon. Pressure upon the cæcum forced gas through the ileocecal valve into the ileum for 6 cm., and into the stomach. By constricting the opening into the stomach the gas was forced up the ileum. The esophageal end of the stomach was severed and water introduced; the fluid distended the stomach slightly but the greater portion flowed through a gastroileostomy opening at the greater curvature of the stomach (Fig. 3), and ran through 6 cm. of the ileum into

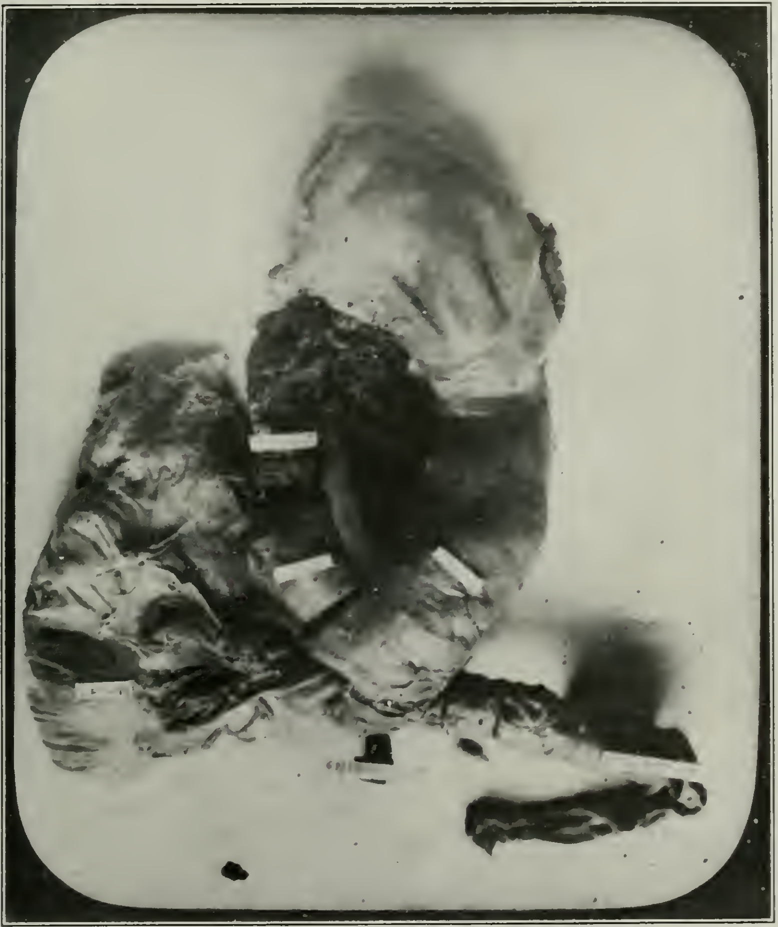


Fig. 3. Photograph of the stomach, ileum and cæcum, showing the gastroileostomy 6 cm. from the ileocæcal valve.

the cæcum. Very little of the fluid passed up the ileum from the enterostomy opening. When the stomach was opened its mucosa was covered with mucus and the mucosa appeared thickened. Upon the greater curvature 6 cm. from the pyloric valve there was noted a large gastroenterostomy opening which easily admitted the index and middle fingers. By separating the fingers one passed down the ileum and the other up the ileum. The opening down the ileum was the larger and more direct. Between the fingers a transverse groove of scar tissue was felt. Externally the gastro-ilial junction was perfect, showing no irregularities nor adhesions. The pyloric opening of the stomach admitted a probe 0.3 cm. in diameter. When the pyloric ring and duodenum were opened the mucosa of the duodenum near the valve showed a papillary adenoma 1 cm. long. The remainder of the duodenal mucosa was unaltered. The bile ducts were patent. The muscular walls of the duodenum were hard and thickened, and externally there were some firm adhesions which constricted the lumen near the pyloric valve. The jejunum and ileum were empty, and apparently smaller in diameter above the anastomosis than below it. The colon was dilated and its mucosa presented numerous mucous folds not unlike the plica intestinales of the small intestines. The lymph follicles of the colon were hypertrophied.

The only other pathology worthy of note was, briefly, a small heart with a relatively hypertrophied left ventricle; right apical pleuritic adhesions; terminal broncho-pneumonia; atrophic spleen and fatty liver; a marked chronic glomerulo-nephritis with both kidneys small, granular and a combined weight of only 130 gm. Both contained numerous small cortical cysts.

Microscopic sections through the gastroileostomy union showed the immediate gastric mucosa excessively infiltrated with mononuclear cells and the immediate mucosa of the ileum showed a similar condition. The epithelium seemed uninterrupted from the mucosa of the stomach to that of the ileum with intestinal glands over the site of the anastomosis. No marked differences were recognizable between the mucosa of the ileum above the anastomosis from that below the anastomosis and in the functioning part of the intestines. The muscular coats presented a band of hyaline scar tissue at the point of the operation. The muscularis mucosæ in the functioning portion of the ileum appeared hypertrophied.

The kidneys showed an extensive chronic glomerular nephritis with relatively few apparently functioning glomeruli present. The presence of the nephritis, clinically, was not suspected, as the blood urea was only 0.3 gm. per liter with a faint trace of albumin and few casts present in the urine without other nephritic symptoms.

The short-circuited alimentary tract was not diagnosed antemortem, and no studies upon the patient's utilization of the dietary elements were made. A brief review of the rather extensive studies upon the utilization of food following resection, or short circuiting of the intestines is of sufficient interest, and follows.

In the works of Flint (1), Erlanger and Hewlett (2), Carrel, Meyer and Levene (3), and Underhill (4), excellent contributions have been made upon the metabolism after resection, or short circuiting, of the small intestines. Flint's studies consisted chiefly of the morphological changes found as a result of abbreviating the intestinal tract and he reported chiefly a transverse hypertrophy involving the muscularis mucosa of the remaining functionating intestine and an apparent atrophy of the non-functioning part. His observations are in accord with those of Cunningham upon this same condition. Flint noted a hypertrophy of the villi and glands of the functionating intestines but no hyperplasia of these structures was observed which is contrary to the statement of Monari, who noted a hyperplasia of the villi and crypts in the remaining part of the intestinal tract following a resection. Flint also noted an increase in the size of the epithelial cells of the glands and many goblet cells were observed in the crypts of the mucosa. This compensatory hypertrophy, Flint concludes, makes it probable that in favorable cases approximately the original epithelial area of the intestine is restored. He further states that the stomach and colon have no power of adaptation to assume the function of the small intestine, although in some cases a marked dilatation of the stomach was observed. The other organs remained unaltered microscopically and macroscopically. Flint's observation upon the metabolic changes following resection, or short circuiting, of the small intestines showed that as much as 50 per cent. of the total amount in a dog may be removed without fatal results, the animal gradually returning to its normal weight and metabolism when upon a favorable diet under good conditions. Removal of 75 per cent. or more, is not necessarily fatal, but such animals rarely show a true recovery. At first the animals suffer from a severe diarrhea and have an enormous appetite and an intense thirst. They lose body weight and remain intensely sensitive to unfavorable conditions of diet and living. They may eliminate as much as 66 per cent. of the food eaten. Compensation, however, will be established upon a rich, easily consumed diet. Any increase in the amount of fats in the food may lead to an increased elimination of fats and nitrogen to about 25 per cent. above normal.

Underhill found that as much as 39 per cent. of the small intestines of a dog may be short circuited without causing significant detrimental changes in the utilization of the various food stuffs, and the animal may gain in weight. This was equally true when the observations were made at a period shortly after operation, or at a period several months later. When as much as 66 per cent. of the small intestines was functionally resected the nutritive condition of the animal was affected. The fat utilization was decreased and the dog displayed a decided tendency to furnish a negative nitrogen balance. There was a small but progressive loss of weight. The food utilization was in general apparently better immediately after the operation than later. In neither of the above animals did a natural increase in fat intake cause significant changes in the utilization of this, or other foodstuff.

When about 75 per cent. of the small intestines of a dog were short circuited, food utilization was more seriously impaired, at least at a period several months after the operation. This is particularly true for fat utilization.

All of these animals displayed a greater ability to utilize carbohydrates than does a normal dog, even though the carbohydrate intake is large. Carbohydrate utilization was complete either shortly after the operation, or months later. This ability to utilize carbohydrates has been a uniform finding among most of the observers.

Over forty human cases are reported in the literature where large portions of the small intestines have been resected and upon whom metabolic studies have been made. Human cases behave in general like the lower animals and show the similar clinical and metabolic disturbances. Noteworthy are the cases of Panchet (5), Axhausen (6), Storp (7), Denk (8), Fantino (9), Zeidler (10), Zusch (11) and others. Zusch (11) reported a case where 316 cm. of the small intestines was functionally resected in which 13.7 to 21.3 per cent. of the diet nitrogen, 18.1 to 38.5 per cent. of the diet fat, and no carbohydrate foods were found in the feces, without evidences of intestinal putrefaction. Other reports show varying degree of functional disturbances in patients following extensive resection. The disturbances may consist simply of a frequency of bowel movements to severe diarrheas of large watery stools. Again some gain in weight and strength while others die from inanition.

The interesting physiological features in our patient were the gain in weight and strength for a period of three years after the operation, without apparent clinical symptoms save a frequency in bowel movement and an increased susceptibility of the intestinal tract to diets rich in fats and indigestible material, also an apparent tolerance for carbohydrate foodstuffs. In the last two years the sensitiveness to a change in diet became exaggerated, associated with a progressive loss of weight and of strength, with an intense desire for food and water. This change probably was the result of a gradual closure of the pyloric passage with an increased loss of small intestinal surface until practically only the terminal 6 cm. of the ileum was functionating.

This case is another one of the rare instances in medicine where a large amount of animal experimentation is to some extent confirmed by the observation of a human case.

References

1. J. M. Flint: *Trans. Conn. Med. Soc.*, 1909, p. 283.
2. Erlanger and Hewlitt: *Am. Jour. Phys.*, 1901, vi, 1.
3. Carrel, Meyer and Levene: *Am. Jour. Phys.*, 1910, xxv, 437.
4. Underhill, F. P.: *Am. Jour. Phys.*, 1910–11, xxvii, 356.
5. Panchet: *Gaz. d. hôp.*, 1905, xxviii, 1667.
6. Axhausen: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1909, Bd. 21, 275.
7. Storp: *Deutsch. Zeit. f. Chir.*, 1907, Bd. 87., 313–329.
8. Denk: *Wien. klin. Wchnschr.*, 1907, xx, 1649.
9. Fantino: *Riforma Med.*, 1902, l, 38.
10. Zeidler: *Zentralbl. f. Chir.*, 1906, xxxiii, 687.
11. Zusch and Barth: *Deutsch. med. Wchnschr.*, 1909, xxxv, 509.

EXPERIMENTAL STUDIES IN ENCEPHALITIS LETHARGICA

LEO LOEWE, M.D., AND ISRAEL STRAUSS, M.D.

(*From the Pathological Laboratory of the Mount Sinai Hospital, New York City*)

During the course of investigations carried on within the past year, Strauss, Hirshfeld and Loewe (1), and Loewe, Hirshfeld and Strauss (2) demonstrated that epidemic encephalitis was due to a filtrable virus. This naturally suggested the application of methods for the cultivation of the filtrable virus. Our early findings on the organism were embodied in a brief preliminary note which appeared in the *Journal of the American Medical Association*, 1919, lxxiii, 1056 (3). It is our intention to present the experimental work upon which the preliminary report was based and to report additional investigations carried on since that time.

Pathology

The gross appearance of the brain of a case of encephalitis is characterized by intense congestion of the pia-arachnoid, and there are small areas which seem to be deposits of fibrin upon the pia.

The histology of acute epidemic encephalitis or encephalitis lethargica is very similar, if not identical, to that of acute poliomyelitis. The difference between the two diseases is chiefly one of degree and localization of the lesion. The principal feature is a round cell infiltration of the so-called perivascular space or more correctly the Virchow-Robin adventitial space. The veins are more affected than the arteries. In relation to the vessels there are foci of small round cells of varying extent which are probably formed by the migration of these cells from the vessels into the parenchyma. Very frequently there are minute hemorrhages and occasionally the hemorrhages are of macroscopic size. In one case there was a hemorrhage of considerable extent in the centrum semiovale which had ruptured into the ventricle. There are areas of edema and microscopic areas of necrosis. The meningitis is characterized by the presence of small round cells. The lesions occur not only in the cerebrum, pons, and medulla, but also in the cord and the posterior root ganglia.

While it is doubtful whether there is any difference between the histology of encephalitis and poliomyelitis, a distinction can be made between the two diseases in the localization of the lesions. The meninges of the cerebrum are more affected in encephalitis than in poliomyelitis. In poliomyelitis it is rare to find extensive lesions in the cerebrum, while in encephalitis the basilar ganglia and midbrain are markedly affected. The pons and medulla are involved in both diseases about equally.

Pathology of Animals

The brains of both monkeys and rabbits are intensely congested. There is a meningitis of varying intensity but always characterized by a predominence of small round cells. In many cases polymorphonuclear leucocytes are almost entirely absent in the inflamed pia. The vessels are dilated and congested. In some of the rabbits, especially those injected with 1 c.c. of spinal fluid, there are extensive subpial hemorrhages. The lesions in the brain are similar to those found in the human, namely, infiltration of small round cells in the Virchow-Robin spaces, focal infiltrations, microscopical hemorrhages, areas of necrosis, and edema. In some of the rabbits there are microscopical areas of focal necrosis in the subcortex in which there are peculiar cells the exact nature of which we have not as yet determined. In some of our animals the most marked lesions occurred in the basilar ganglia, pons, and medulla, and this is especially true of a monkey and rabbits inoculated with the germ. The filtrate from the nasopharyngeal membrane of a fatal case named "W" when injected intracerebrally into rabbits, killed the animals very quickly and produced a meningitis and extensive hemorrhages. Subsequent inoculations of filtrates of these brains into other rabbits caused an apparent lessening of virulence of the virus, the rabbits lived longer, and the lesion became less hemorrhagic and more typical until finally we obtained the classical picture of small round cell infiltration in the Virchow-Robin spaces, and focal infiltrations with very few, if any, hemorrhages. This particular virus therefore produced in the rabbit, first, a pathological picture of a hemorrhagic encephalitis and subsequently the lesion which we are accustomed to regard as more characteristic of epidemic encephalitis.

As is well known to investigators, rabbits that die as the result of experimentation, show very few symptoms of disease before death. They are usually found dead by attendants who make rounds of the cages. This has been true of all of our inoculated rabbits with two exceptions:

R. 29, which had received a filtrate of the brain of monkey 12, was discovered apparently dead by the attendant and placed in the ice box. Fortunately we were notified of its demise and went to autopsy it. We found the rabbit was still alive, but the respirations were so shallow that it was not surprising the attendant was deceived. The animal lay on its side with eyes closed, legs extended and head drawn back. We kept it alive four days by feeding it by gavage. It died in a convulsion. The virus from this rabbit's brain was carried through four generations.

R. 52 presented a similar clinical picture and we kept it alive by gavage for six days. The virus from its brain was carried through three generations.

The picture presented by these two rabbits was strikingly like the lethargy we have observed in our human cases.

Inoculation Experiments

We began our experiments March 1, 1919, by inoculating a *Macacus rhesus* monkey subdurally and intraperitoneally with a saline emulsion of human brain from an encephalitis case. The following day the animal was ill and its spinal fluid contained 90 mononuclear cells per c. mm. Two days later, fearing that the animal might survive, we killed it. Sections of the brain showed multiple cortical and subcortical punctate hemorrhages, and microscopically there was perivascular infiltration of mononuclear leucocytes and a moderate degree of meningitis shown by an infiltration of small round cells. An emulsion of this monkey's brain was then injected intraperitoneally and *intracerebrally* into another *Macacus rhesus* and no symptoms developed until six days later when the animal became paralyzed on the side opposite the site of injection. It was killed seven days later, or thirteen days following inoculation, and there was found a large hemorrhage surrounded by an area of necrosis at the site of the injection which had been made in the neighborhood of the motor pathway. The half of the cerebrum which contained the lesion was put in formalin and the other half in 50 per cent. glycerin in cold storage. Two months later sections were made and showed the presence of a meningitis with mononuclear cells and of perivascular infiltration around vessels at a distance from the hemorrhagic and necrotic area. (See figs. 4, 5, and 6.) This convinced us that the inoculation had probably been successful. We therefore made an emulsion of the glycerinated brain and inoculated a monkey intracranially. Aside from a slight apathy this monkey showed no symptoms. Two rabbits were inoculated with the same emulsion: both died. One showed no cerebral lesion, but the other showed the typical lesions of encephalitis. We had therefore succeeded in transmitting the virus through two monkeys and a rabbit and had further proved that the virus remained viable for two months in 50 per cent. glycerin. It became evident also that the monkey was not very susceptible to the virus obtained from the brain and that inoculation from brain to brain was difficult, and that the virus of the disease resided in the naso-pharynx. The next logical step was for us to investigate along this line.

We chose a case where the nasal discharge was very profuse, thick and mucopurulent. This discharge was emulsified with saline solution and passed through a Berkefeld filter "N." Cultures on ordinary media showed it to be sterile. A *Macacus* was inoculated intracranially and intraperitoneally. Eight days later both hind legs were paretic and the animal was distinctly apathetic. Fourteen days after inoculation the spinal fluid contained 16 cells per c. mm., mostly lymphocytes. By the eighteenth day it had completely recovered. Two months later this animal was inoculated intracranially with a filtrate of nasal mucous membrane which had produced lesions in monkeys and was very virulent for rabbits. We used what we judged to be three times the lethal dose. The animal gave no evidence of disease. It had probably acquired an immunity.

Having found the virus in the nasal discharge it was decided to use the naso-pharyngeal mucous membrane of a fatal case for inoculation. This was ground up in a mortar in saline solution and filtered through a Berkefeld filter "N." The filtrate was found to be sterile on ordinary media and on April 7, a *Macacus* was inoculated intracranially and intraperitoneally. The following day there was a right hemiparesis and paresis of the left external rectus. Three days later there were typical Jacksonian convulsions of the right side which later became general, and stupor. These convulsions continued two days and the animal became very weak. It was killed on April 13, six days after inoculation. There were numerous cortical and subcortical hemorrhages; one on the surface of, and a large one within, the pons. There was some necrosis and glia cell increase near the hemorrhage. The pathological picture was that of a hemorrhagic encephalitis. An emulsion of this brain was injected intracranially into another monkey and two days later there was paresis of the right arm and leg. The animal was then killed and the brain showed intense congestion, a large hemorrhagic area surrounded by numerous cortical and subcortical punctate hemorrhages, and a small area of necrosis in the center of the large hemorrhage. Again the picture of a hemorrhagic encephalitis. While in these two monkeys the typical histological picture of epidemic encephalitis was not present, we believe the lesion was due to the virus of the latter disease, for as pointed out before, we have experimental proof that the virus can first cause hemorrhages and then later probably through loss of virulence produce the typical histological picture of mononuclear meningitis, perivascular, and focal infiltration of small round cells.

We inoculated another monkey with the filtrate of naso-pharyngeal mucous membrane. It developed a paresis of both hind limbs, and was very ill for four weeks and then recovered. Another monkey was inoculated with the same filtrate after it had been kept in 50 per cent. glycerine in cold storage for two months. It showed marked excitability, ruffled fur, and paresis of left foreleg. It recovered in four weeks.

Control Experiments

One monkey was inoculated with 2 c.c. of the filtrate from the nasal washings of a case of influenza complicated with sinusitis and broncho-pneumonia with a negative result.

Three other monkeys were inoculated intracranially with filtrates of naso-pharyngeal mucous membranes from cases which died from surgical diseases. They were all negative.

Our investigation soon showed that rabbits were much more susceptible to the virus than monkeys. By the time we discovered this it was too late to try inoculation of human brain emulsions in these animals. Recently we have obtained fresh material from the cases, and the following results were obtained.

	No. Cases	Rabbits Inoculated	No. Dead	No. Rabbits with Lesions
Filtrate of human brain....	3	12	4	3
Emulsion of human brain..	2	6	4	2

The filtrate from the nasopharyngeal mucous membrane of a fatal case has been inoculated in a rabbit intracranially and produced typical lesions. This virus has been transmitted through six rabbits, the filtrate of a brain emulsion being used each time. It was then transmitted successfully to a monkey and back to the rabbit for two transmissions. We then stopped because we could see no reason for further propagation.

A glycerinated filtrate of nasal pharyngeal mucous membrane which had been kept in cold storage for two months has been transmitted successfully through three rabbits, and the same filtrate which had been kept four months in cold storage was transmitted through four rabbits. This virus was the one which first caused hemorrhagic lesions and subsequently in later rabbits the typical lesions.

Control Experiments

Filtrates of nasopharyngeal mucous membrane of five fatal cases dying from surgical conditions and one case dying from mediastinal tumor were injected intracranially in rabbits with negative results.

We have taken the naso-pharyngeal mucous membrane of rabbits succumbing to inoculations of the virus and made filtrates which have been inoculated into rabbits with positive results. As controls to these experiments, we have inoculated seven rabbits with filtrates of nasopharyngeal mucous membrane of rabbits with negative results.

Our investigation seems to point rather conclusively to the nasopharynx as the portal of entry of the infection and in the few experiments which we have made thus far it seems also indicated that the virus can be excreted by the nasopharynx. Our clinical experience likewise points to the nasopharynx as the portal of entry for the infection. Many of the cases give a history of coryza and sore throat before the onset of the symptoms of encephalitis and not infrequently the symptoms of a mild sinusitis are complained of. We have seen three cases where a specialist on diseases of the nose and throat had been consulted because of the nasal discharge and pain in the face, and suspected a mild sinusitis which was probably present though subsequently the development of the symptoms of encephalitis made the case clear.

Normal saline solution is used in washing the nasopharynx and the solution is filtered through Berkefeld "N" very shortly after it is obtained. The filtrate is then cultured on ordinary media and if sterile 1 c.c. is injected intracranially into two or three rabbits. The results of these inoculations are as follows:

No. Cases	No. Rabbits Injected	No. Rabbits Dead	No. Rabbits with Lesions	Diag. Made in Cases	Time	Average	Per Cent.
18	38	28	17	14	1–7 days	3 days	78

The inoculation intracranially into rabbits of filtrates of nasopharyngeal washings has become in our hands a method of diagnosis. As noted it is a method which gives a positive result in 78 per cent. of cases. There are cases of encephalitis which do not present the classical symptoms of encephalitis and it is in such cases that rabbit inoculation has been especially valuable.

Spinal Fluid Inoculations

Inoculation of spinal fluids has demonstrated that the virus is present in the fluid. One *Macacus rhesus* received intracranially 2 c.c. of the spinal fluid of a fatal case of encephalitis, and developed a paresis of the right hind leg. It showed very marked motor excitability which was followed by a period when it was very apathetic. It appeared ill for four weeks but completely recovered at the end of six weeks. Another monkey received 2 c.c. of spinal fluid which had been kept on ice for nineteen days, and which had been obtained from a case which subsequently recovered. This inoculation was negative.

Inoculations into rabbits proved more successful and we have used this method in conjunction with inoculation of nasal washings for diagnosis. The results of these experiments are as follows:

No. Cases	No Rabbits Injected	No. Rabbits Dead	No. Rabbits with Lesions	Diag. Established	Time	Average	Per Cent.
26	56	38	22	16	1–8 days	3 days	61

As a control we inoculated ten rabbits with spinal fluid from cases of cerebral neoplasm, uremia, brain abscess, and psychasthenia. These inoculations were negative.

In the beginning we inoculated rabbits with 1 c.c. of the spinal fluid from encephalitis cases and found that the animals died within 12 hours and showed nothing but congestion or subpial hemorrhages, but not the typical histological lesions. We then reduced the dose to 1/4 c.c., the animal lived longer, and we obtained the definite pathological picture. It would appear from this that the spinal fluid of these cases contains some toxic substance to which the rabbit is very susceptible, but we have not as yet been able to determine its nature.

Relationship to Poliomyelitis

When the epidemic of acute encephalitis first made its appearance in England opinion was divided as to whether one had to deal with botulism, poliomyelitis or a new disease. Botulism was quickly ruled out, and later it was seen that the clinical picture was not the same as that with which physicians had become familiar in the epidemics of poliomyelitis in recent years. The predominance of cerebral symptoms, and under this category are to be included the basilar ganglia and mid-brain, indicated either a new disease entity or a modification of the poliomyelitic virus, both as to its virulence and its affinity for the bulb and spinal cord. Our investigations seem to prove that we are dealing with a new clinical entity. We have found in our inoculations of monkeys both with virus and with cultures of the organism that they are extremely refractory. Some of the animals have become ill and then recovered, others have shown no evidence of illness. As is well known, monkeys are peculiarly susceptible to the virus of poliomyelitis and generally succumb to the inoculation. It is unusual for them to recover and have a natural immunity. Marks succeeded in infecting rabbits with inoculations of poliomyelitis virus. He did not produce the typical lesion of poliomyelitis, but was able to transfer the disease from rabbit to monkey. It appears from his experiments that the rabbits acted as a host for the virus. Our investigations show that rabbits are very susceptible to the virus and organism of encephalitis, although approximately 50 per cent. appear to have a natural immunity. Those that do succumb show the lesions which are typical of the disease. No one so far as we are aware has ever succeeded in producing poliomyelitis experimentally by inoculation of spinal fluid. We have succeeded, not only in our inoculation experiments, but also in isolating the organism from the spinal fluid. Therefore we feel justified in concluding not only on clinical grounds, but also from our animal inoculations and cultures, that acute epidemic encephalitis and acute poliomyelitis are two distinct diseases.

Relationship to Influenza

During the epidemic of influenza in the fall of 1918, there were a number of cases of encephalitis. These cases increased in frequency, however, during the months of January, February and March, 1919, after the peak of the influenza epidemic had been reached. During the summer there appeared a number of sporadic cases of encephalitis, and in the early fall the number appeared to be on the increase, until the onset of the second influenza epidemic when there was a marked rise in the incidence of the disease. However, just as in the previous year, so again it has been noted that the greatest number of encephalitis cases appeared after the influenza epidemic had reached its height, and was on the wane. Many of the cases of encephalitis give a history of previous influenza infection antedating the onset by a period varying from a few weeks to a few months. Some cases have developed during the convalescence period of what had been diagnosed as an influenza infection. It would appear, therefore, that either influenza bears some etiological relationship to encephalitis, or that it renders individuals apparently more susceptible to the disease, or that the two appear to run a synchronous course.

The animals in which we have produced encephalitis have shown no lesions which we can consider of the nature of influenza. It is extremely difficult to determine the relationship of these two conditions until we know definitely what is the etiological factor in influenza. In three cases we have isolated from filtrates or nasopharyngeal washings, organisms in pure culture which closely resemble morphologically the organism found in our encephalitis series. This work is now being prosecuted

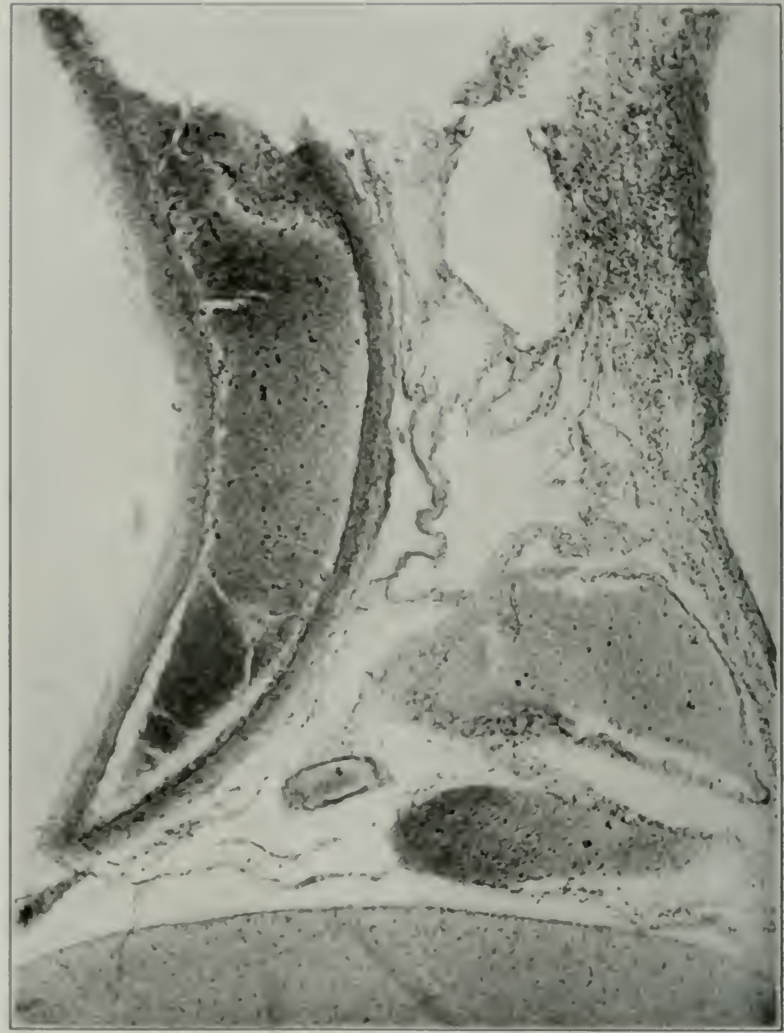


FIG. 1. Human brain. Mononuclear cell infiltration and congestion of vessels in meninges of cerebrum.

vigorously, to establish a possible etiologic relationship. Thus far no encephalitis has been produced in rabbits with these strains.

Cultivation of Organism

The negative results of our early cultural studies using ordinary laboratory media for aerobic and anaerobic culture, as well as the Rosenow technic, soon convinced us that we were dealing with an organism of very discriminating cultural requirements. This led us to the adoption of the tissue ascitic fluid medium introduced by Smith, popularized by Noguchi and so successfully used by him for the cultivation of *Treponema pallidum* and other

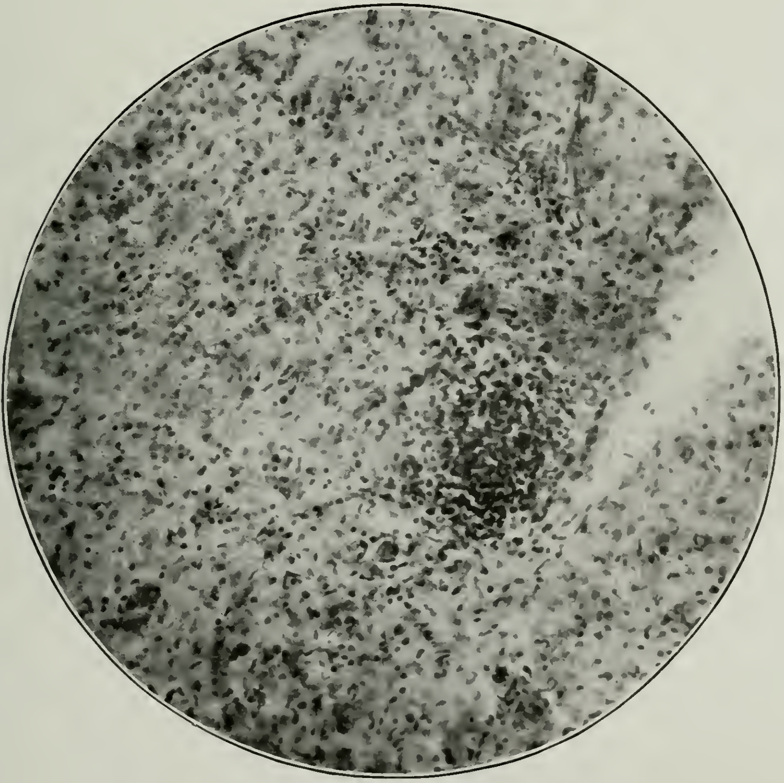


FIG. 2. Human brain. Focal infiltrations with mononuclear cells in the putamen (lenticular nucleus).

organisms, and by Flexner and Noguchi in growing the globoid bodies of poliomyelitis. The original Noguchi technic has been followed closely, the various modifications which suggested themselves having been found unsatisfactory. The preparation of the medium as now used is briefly as follows:

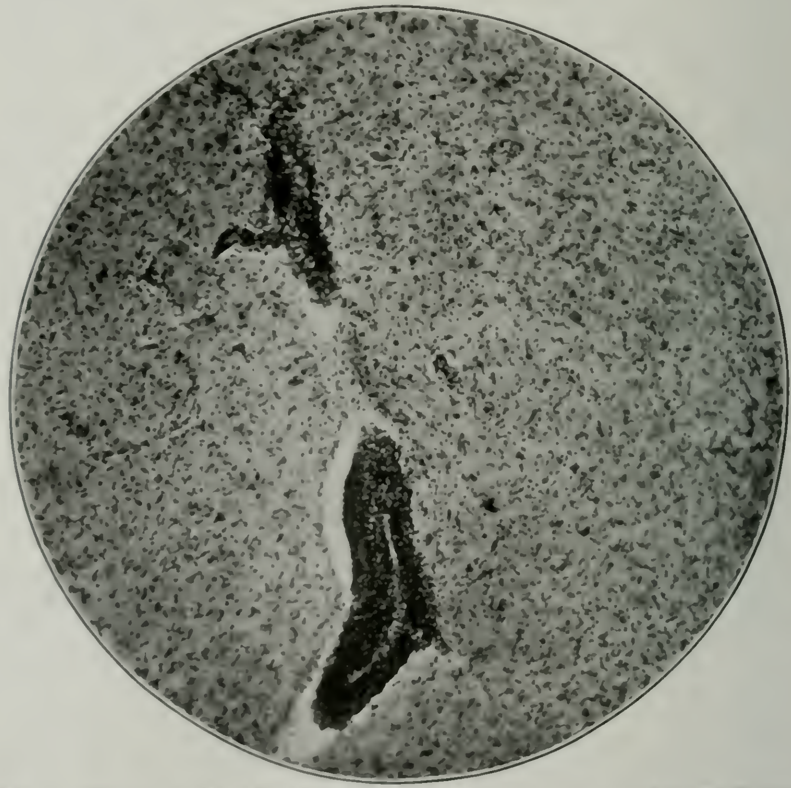


Fig. 3. Human brain. Mononuclear cell infiltration in the Virchow-Robin and perivascular spaces of vessel in the tegmentum of the mid-brain.

Sterile kidney fragments are transferred to tubes 20 cm. x 1½ cm., covered with 3 to 4 c.c. of sterile ascitic fluid, and incubated for 48 hours. At the end of this time the contaminated tubes are detected by gross examination and by dark field illumination and forthwith discarded. The sterile tubes are then inoculated and ascitic fluid added to form a column about 10 cm. high. Vaseline of a low melting point is heated and poured over the surface of the fluid in a layer about 1 cm. thick. The vaseline quickly cools and effectually seals the tube thus producing almost perfect anaerobic conditions.

Control tubes are set up as follows: (1) Serum and vaseline, (2) inoculum, serum and vaseline, (3) serum, kidney and vaseline. Both controls and inoculated tubes are incubated at 37° C.

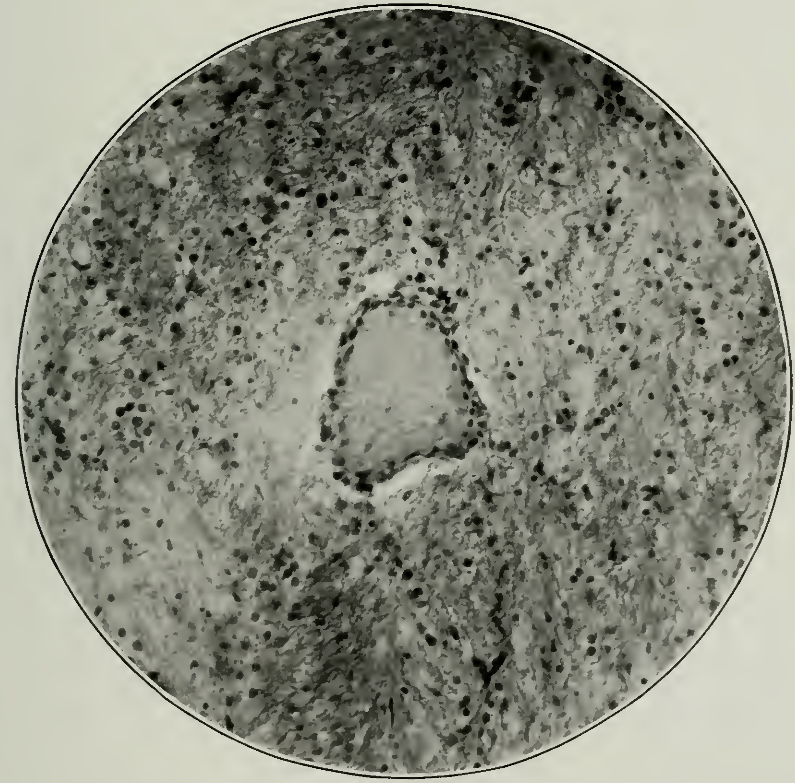


Fig. 4. Monkey brain. Edema, necrosis and adventitial infiltration of vessel in cortex. Animal injected intracerebrally with emulsion of brain of monkey successfully inoculated with infected human brain.

The optimum solid medium is of a gelatinous consistency, made so by the addition of one part of 2 per cent. nutrient agar to four or five parts of ascitic fluid, the kidney tissue being added as usual. The customary controls are also made.

The materials cultured were as follows:

1. Fragments, saline emulsions, and Berkefeld filtrates of saline emulsions of brains of humans and of experimental animals. Brain material was taken preferably from the mid-brain where the most pronounced lesions of this disease are found. Material for inoculation was removed under the strictest sterile precautions and with the brain *in situ*. Grossly contaminated material has been stored in the refrigerator in 50 per cent. glycerin, and subsequently cultured *en bloc* or ground up and filtered.

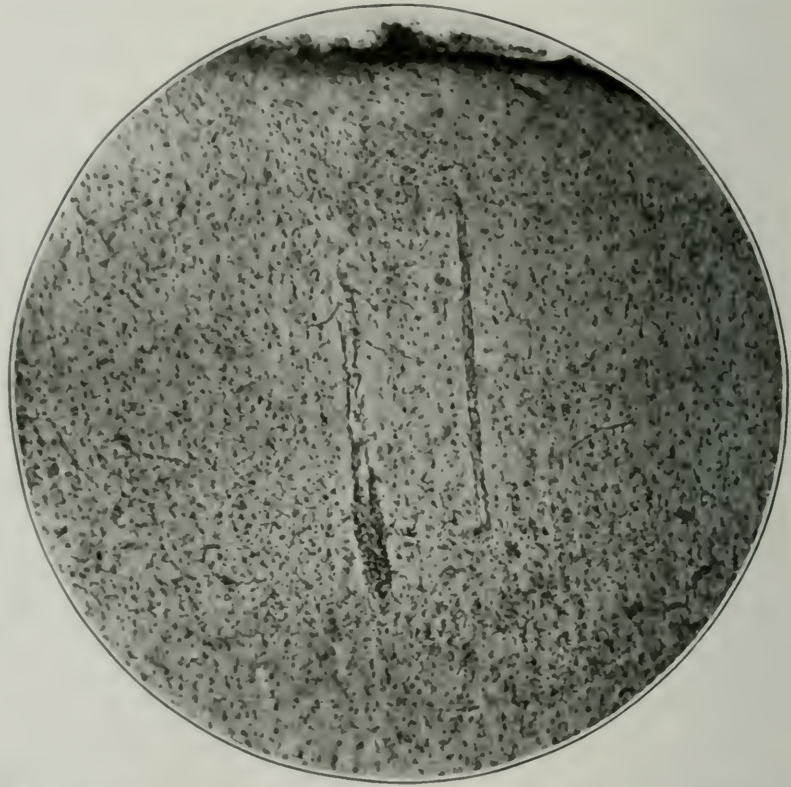


FIG. 5. Monkey brain. Cortex showing perivascular infiltration of mononuclear cells. Animal same as that pictured in Fig. 4.

2. Cerebrospinal fluids removed under sterile precautions from patients and experimental animals were cultured in amounts from 0.5 to 1.0 c c.

3. Nasopharyngeal washings from living patients were fil-

tered through the standard 5N Berkefeld or Mandler filters. Nasopharyngeal mucous membranes removed at autopsy from humans and experimental animals were finely emulsified and filtered.

All filters used held back *B. prodigiosus* under the same conditions obtaining in the experimental filtrations. All filtrates before being used were cultured on ordinary laboratory media to insure sterility.

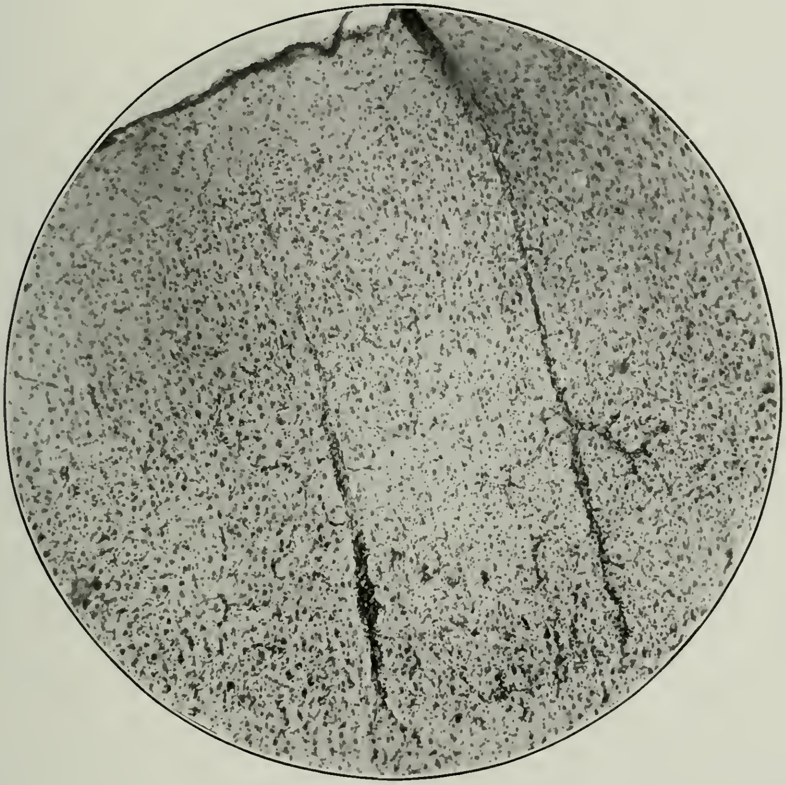


FIG. 6. Monkey brain. Cortex showing perivascular infiltration with mononuclear cells. Animal same as that pictured in Fig. 4.

Control studies were carried out on nasal washings, nasopharyngeal mucous membranes, cerebrospinal fluids and brains of patients suffering from or dead of diseases other than lethargic encephalitis. The nasopharyngeal mucous membrane and brains of normal rabbits were also studied.

In spite of the numerous precautions used in the preparation of the culture tubes, a small percentage of contaminations invariably appear. Most contaminations are detected grossly, by dense clouding of the medium, gas formation, evidence of putrefaction, and the rapid disintegration of the kidney. Others are discovered on dark field illumination and examination of smears stained by the Gram method.

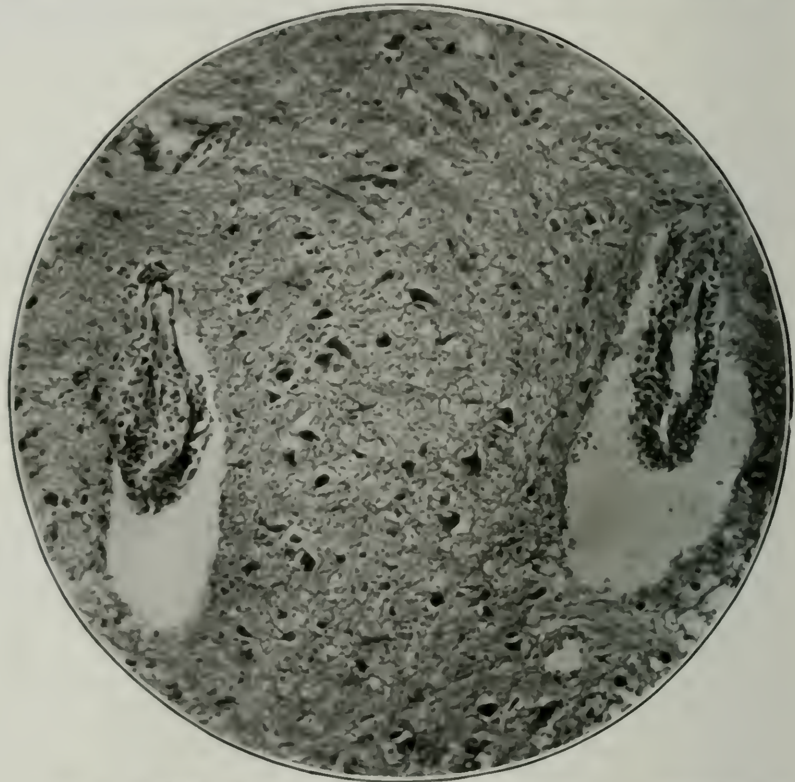


Fig. 7. Monkey brain. Mononuclear cell infiltration in Virchow-Robin space (adventitia). Pons. Animal inoculated with emulsion of brain from human case.

A successful growth is usually manifested on the fifth to the seventh day by clouding of the medium commencing about the kidney tissue, the outline of which becomes hazy and irregular. The clouding extends rapidly upward to within about 1 cm. of the top of the ascitic fluid column. The organisms are not held in suspension long but tend to form clumps which settle to the bottom of the tube, leaving the supernatant fluid clear. The clouding of the medium is due partly to the growth of the organism itself, and partly to protein precipitation due to the acid produced by the organisms.

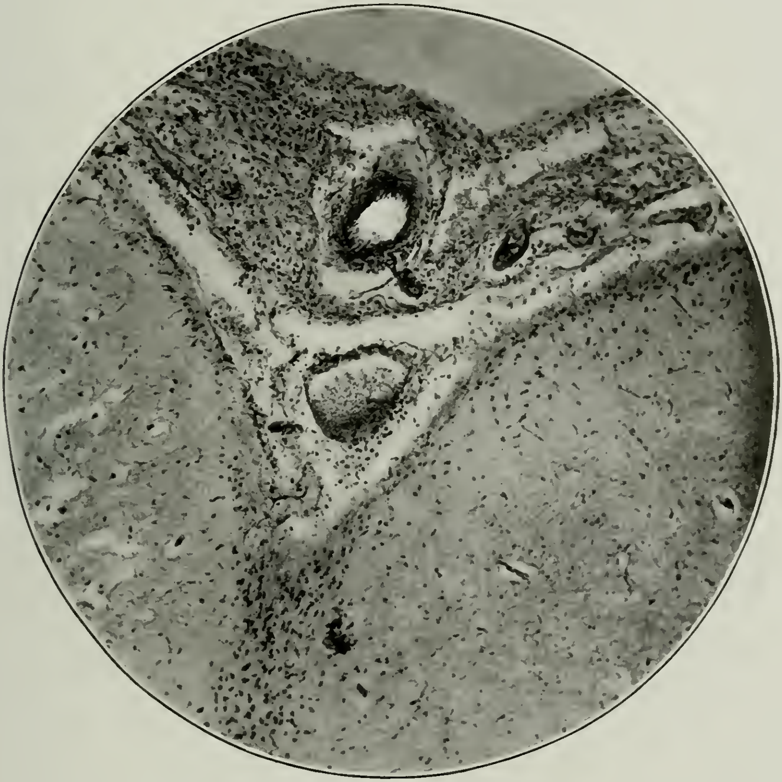


FIG. 8. Rabbit brain. Mononuclear cell infiltration in the meninges of the cerebrum. Animal injected with Berkefeld filtrate of nasopharyngeal mucous membrane from a fatal human case.

Transfer to solid medium can be obtained only with the later generations of the organism. The growth in solid medium assumes different forms depending on the adaptability of the given strain to this type of culture medium. When the organisms are numerous a diffuse clouding is observed, most marked about the region of the kidney and extending upward. When the organisms are fewer in number, minute colonies appear only in the region of the kidney or occasionally scattered throughout the medium. The colonies gradually increase in size so as to become recognizable with the naked eye.

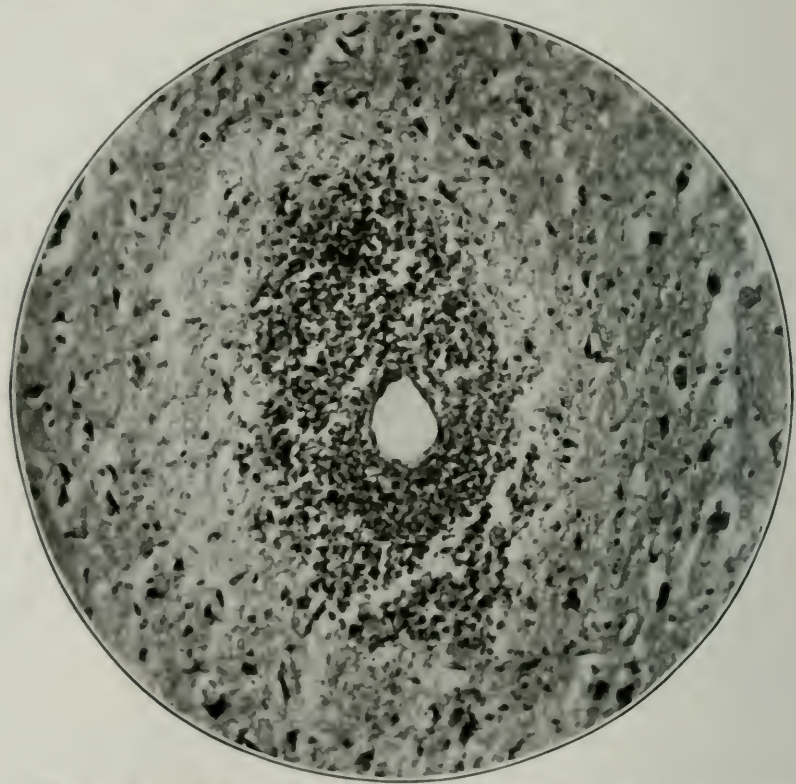


FIG. 9. Rabbit brain. Perivascular infiltration (principally mononuclear cells) of vessels in the mid-brain. Third transmission in rabbit of virus originally derived from human nasopharyngeal mucous membrane.

Studies of fluid cultures under dark field illumination reveal the organism as minute globular refractile forms, occurring singly, in diplo-form, chains and clumps, the latter form predominating, especially in the older cultures. These bodies show active Brownian motion but no true motility.

In stained smears the organisms appear as minute globular bodies which are arranged singly, in diplo-forms, in chains and clusters. The organism has an average diameter of 0.25 micra as measured by the ocular micrometer. The reaction to the Gram-stain depends a great deal on the medium used and on the age of the individual culture. Young cultures and those grown on fluid medium are mostly Gram-positive, while older cultures and those grown on solid media tend at times to be Gram-negative. The organisms stain well with prolonged staining in Giemsa, Loeffler's alkaline methylene blue, Unna's alkaline methylene blue (old) or Ljubinsky's pyoktanin-acetic acid, after fixa-

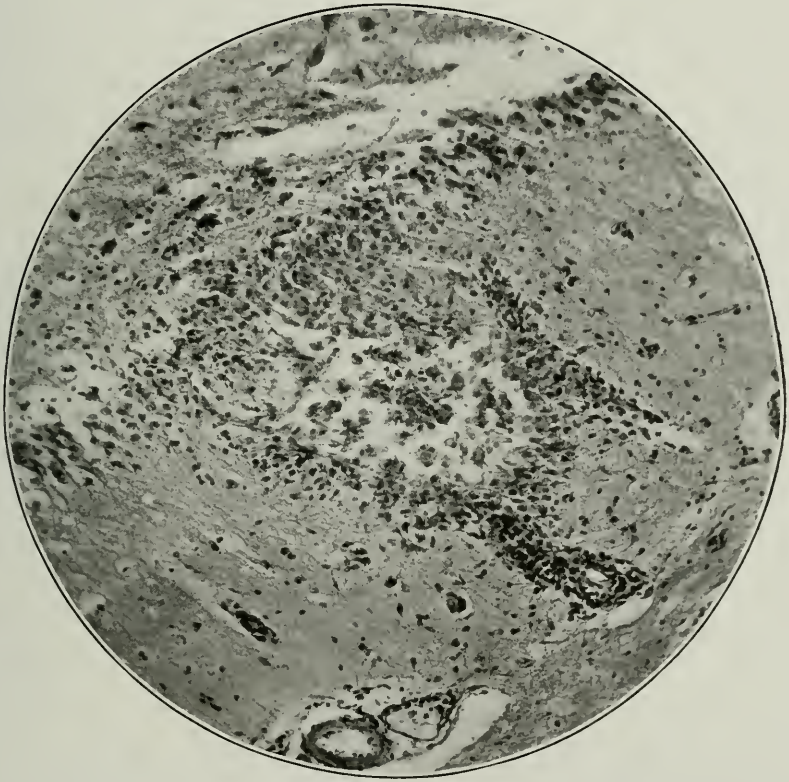


FIG. 10. Rabbit brain. Area of focal necrosis in proximity to vessels showing the perivascular infiltration. Mid-brain. Fourth transmission in rabbit of virus derived from human nasopharyngeal mucous membrane.

tion in methyl or absolute alcohol. These several stains have proved valuable in establishing a definite tinctorial reaction for the organism which is basophilic in nature.

The organism has been recovered in pure culture from Berkefeld filtrates of the nasopharyngeal mucous membrane of four human cases of epidemic encephalitis. We succeeded in all of four attempts. One of these strains has been carried on artificial culture medium without animal passage to the fifteenth generation; another to the tenth Later strains have proven pathogenic

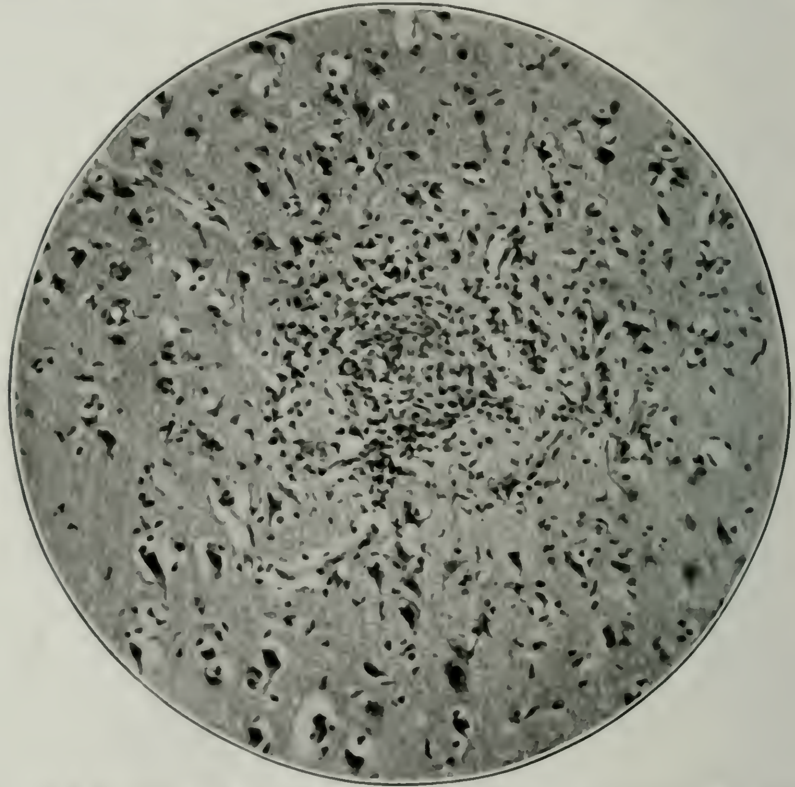


Fig. 11. Rabbit brain. Area of focal infiltration with mononuclear cells in the basilar ganglia. Animal injected with Berkefeld filtrate of brain of monkey successfully inoculated with virus derived from human nasopharyngeal mucous membrane, and which had been transmitted through four generations in rabbits.

for animals. Controls prepared with filtrates of nasopharyngeal mucous membrane of humans dying of such conditions as cardiovascular disease, megacolon, peritonitis, mediastinal tumor, carcinoma of the stomach, post-operative hemorrhage and empyema have all been sterile.

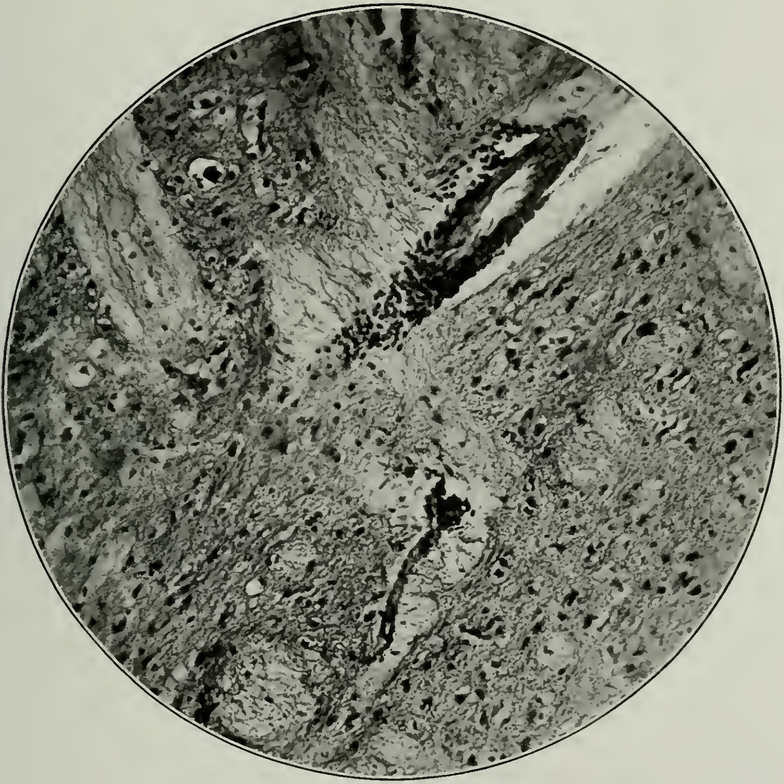


FIG. 12. Rabbit brain. Area of mid-brain showing perivascular infiltration with round cells. Same animal as Fig. 11.

Filtrates of nasal washings from seventeen cases of epidemic encephalitis were cultured with positive findings in eleven cases or 65 per cent. Many of these strains were subcultured successfully and carried along for several generations. The organism was recovered from brains of rabbits injected with virus of these nasal washings in five instances as well as from the brains of rabbits injected with the organisms from these nasal washings

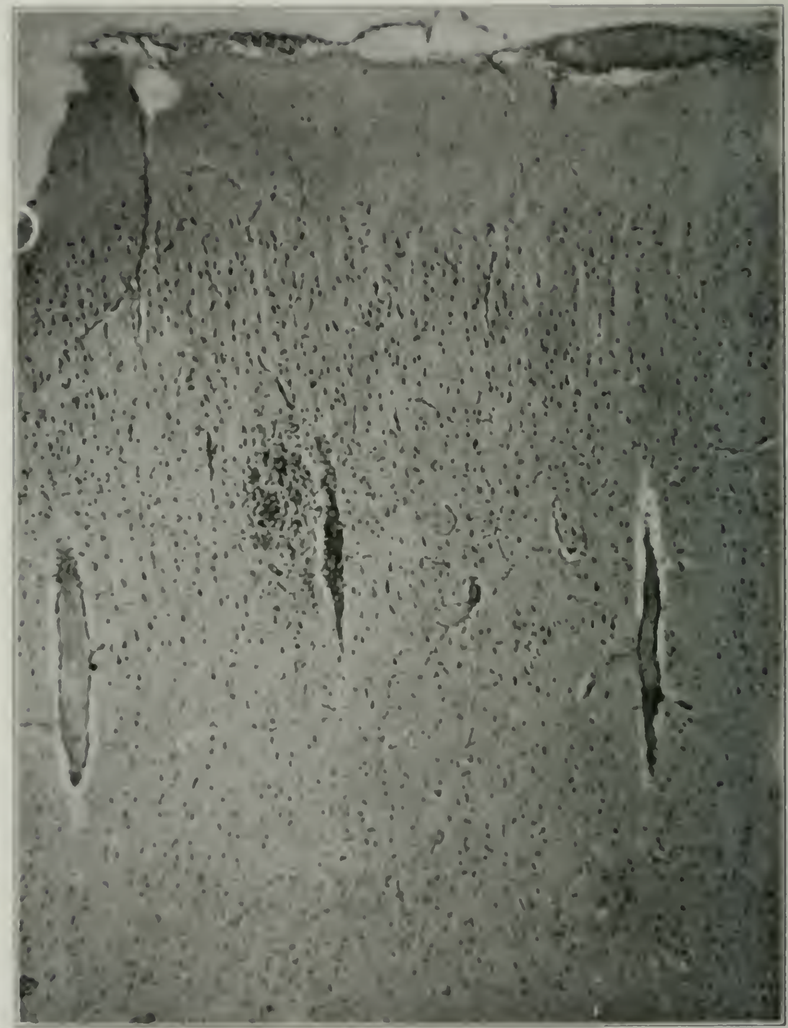


FIG. 13. Rabbit brain. Cortex of cerebrum showing focal infiltration with round cells in proximity to vessel showing mononuclear cell infiltration of the adventitia. Rabbit injected with same inoculum as animal pictured in Figs. 11 and 12.

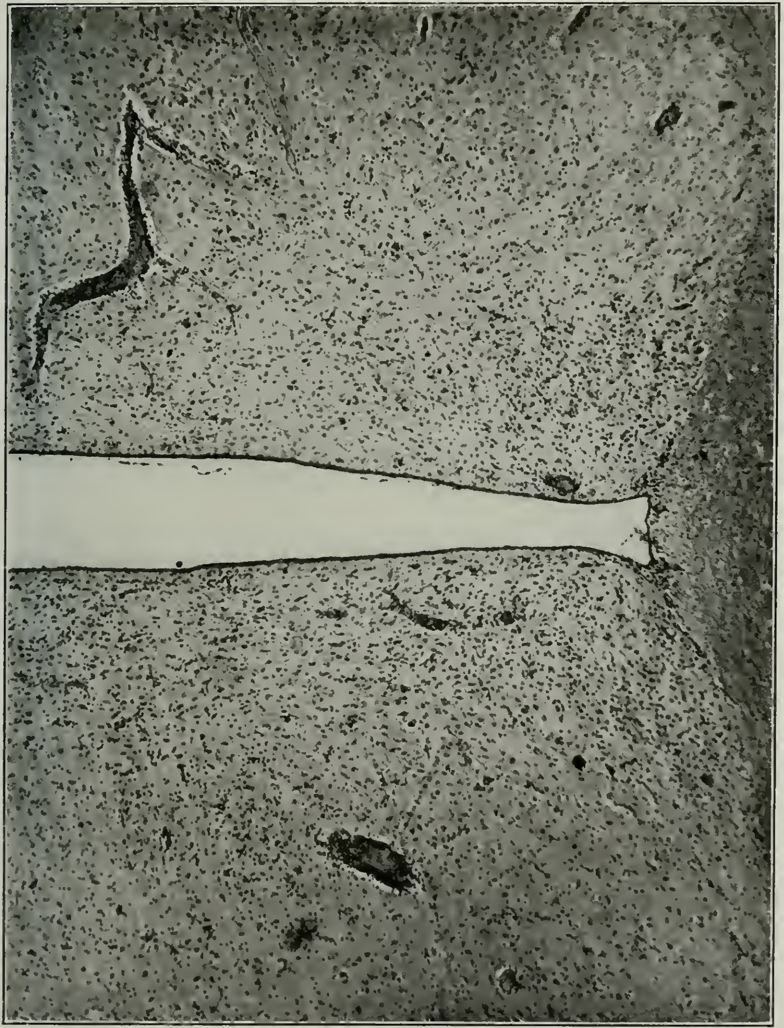


FIG. 14. Rabbit brain. Mononuclear cell infiltration of the parenchyma and of the adventitia of vessels in the basilar ganglia. Animal injected with Berkefeld filtrate derived from nasopharyngeal mucous membrane of animal pictured in Figs. 11 and 12.

in three instances. Control studies of nasal washings were negative in eight instances (mastoiditis (2), sinusitis, pyelitis, appendicitis, empyema, cholelithiasis, nephrolithiasis).

The organism was recovered from the nasopharyngeal mucous membrane of three rabbits which showed typical clinical and pathological pictures after inoculation with human infectious material.

Cerebrospinal fluids have yielded the organism in ten out of twenty cases. It was found in one case on direct smear of the sediment of the centrifugalized spinal fluid. The organism was recovered from the brains of eight rabbits injected with the spinal fluid itself, and from the brains of four rabbits injected with the organisms derived from these spinal fluids. Eight spinal fluids from patients suffering from brain abscess, brain tumor, psychasthenia, uremia, multiple sclerosis, tuberculous meningitis, neurosyphilis and spinal cord tumor, were all cultured with entirely negative results.

A total of 51 rabbit brains was cultured, using Berkefeld filtrates of brain, blocks of brain and emulsions of brain. The organism was successfully recovered from 34 of the 51 brains cultured, or 66 per cent.

A total of six monkey brains from animals injected with various viruses was cultured with five positive results, or 85 per cent. The organism was demonstrated in cultures of blocks of a glycerolated brain kept in the refrigerator for three and a half months. A positive culture was obtained from the brain of a monkey that was injected with the seventh generation of a culture of human nasopharyngeal mucous membrane.

After numerous attempts and by various means we have finally been able to isolate the organism from human brains. We achieved our earliest and best results with a case of lethargic encephalitis that ran a very rapid course—death ensuing in five days. Positive cultures were obtained on the first attempt by the use of large blocks of brain tissue. In another instance, we were able to use only filtrates because the brain was grossly contaminated. It is our impression that the organism exists in the

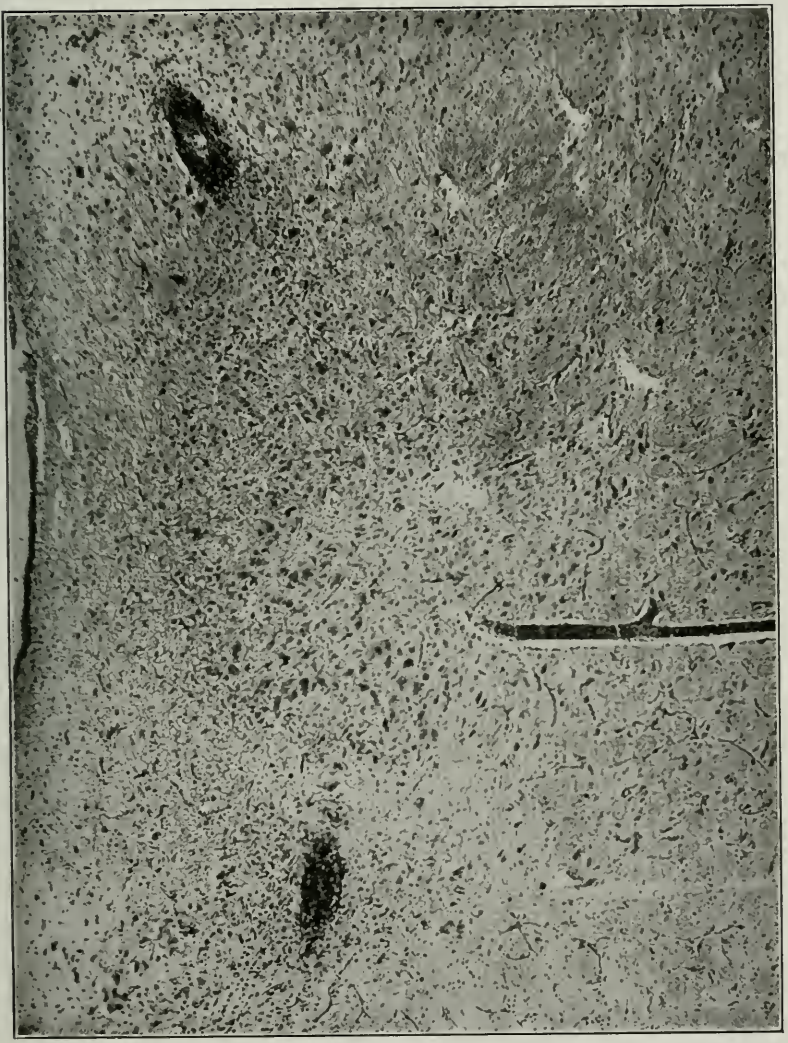


Fig. 15. Rabbit brain. Area of mid-brain showing perivascular infiltration. Animal injected with cerebrospinal fluid from human case.

human brain in an attenuated form or in such small numbers that it is only by persistence and the use of special methods, viz., concentration *in vacuo*, that successful growths are obtained

The seventh generation of a culture, originally derived from a 50 per cent. glycerolated filtrate of human nasopharyngeal mucous membrane, brought down a monkey with the typical clinical and pathological picture. As in the case of the virus, however, monkeys are apparently refractory to this organism.

Our rabbit inoculation experiments have been carried out with a number of strains preferably in the later generations. About 50 per cent. have succumbed with typical lesions. The incubation period varies from 2 to 42 days. The strains used have been two; derived from filtrates of two human nasopharyngeal mucous membranes. Filtrates of cultures from the third to the eleventh generations were injected intracranially into 20 rabbits—12 succumbing with typical lesions. Further successful animal transmissions were made with filtrates of these brains. Cultures derived from the brains of inoculated animals have proved pathogenic for rabbits in approximately 50 per cent. of the rabbits injected.

Colonies picked from solid cultures of these strains have been grown in fluid medium. These cultures injected intracranially into rabbits have produced lesions in five of eight animals.

Cultures of organisms derived from spinal fluids and of organisms isolated from the brains of rabbits injected with these cultures have produced lesions in five of twelve animals inoculated.

We wish to point out in connection with our animal experiments that we have not only produced typical lesions in rabbits with cultures derived from virus of various kinds but have been able in many instances to recover the organism from the brains of animals so injected and to produce again the disease in animals with later generations of these same organisms.

The microorganism which we have isolated resembles in morphology and in cultural characteristics that found by Flexner and Noguchi in poliomyelitis. It differs in virulence, incidence and in the ability to infect rabbits. The isolation of the organism from the spinal fluid sharply differentiated this disease from poliomyelitis.

References

1. Strauss, Hirshfield and Loewe: *New York Med. Jour.*, 1919, cix, 772.
2. Loewe, Hirshfield and Strauss: *Jour. Infect Dis.*, 1919, xxv, 378.
3. Loewe and Strauss: *Jour. Am. Med. Assn.*, 1919, lxxiii, 1056.

Since our article was read we have noted in the Comptes Rendu des Science de la Societe de Biologie, March, 1920, articles by Levaditi and P. Harvier confirming our work. They have succeeded in producing encephalitis in rabbits and guinea pigs by the intracranial and intraocular injection of infected human brain. After a number (7) of passages through the rabbit they found that the virus became pathogenic for the monkey. They agree with us that epidemic encephalitis is due to a specific filterable virus different from poliomyelitis: that it can be preserved in glycerin; and that no organism could be obtained by the ordinary methods. They make no mention of an attempt to cultivate their virus on the tissue-ascitic fluid medium.

Discussion:

Dr. Norris: I want to congratulate Drs. Strauss and Loewe on their notable presentation, and the splendid work which they have done. I think there is no question at all but that they have proved their point, namely, that we are dealing with a filterable virus. I do not feel at all capable of expressing any opinion of the bacteriological work. I have done enough of that work to know how precarious the Noguchi method is, and what care must be used with it. I think as the paper was presented that it would be very ungracious to say that Dr. Loewe has not proved his point, but I think that there is the opening left to me to think that the organism which he has shown on the screen is not the etiological factor, but one which is symbiotic with the filterable virus. That of course is nothing against Dr. Loewe's claim as to the infectivity of his cultures. We must take it for granted that a filterable virus was present in the eleventh generation and that it has been growing in symbiosis with the etiological organism.

Dr. Wood: I have had only three recent autopsies on cases of encephalitis, and what is interesting in the sections of these lesions is their great extent as compared to the human cases. The cortical lesions were very slight in the human brains, although they varied in distribution and in amount, and even in the basal ganglia and pons were less than those shown in the animals.

Dr. Libman: In regard to the point Dr. Norris made, I am not sure that it is correct. Even if one assumed that the organism one sees in these cultures is not the agent of the disease, but that the agent is in the fluid part of the culture, the fact would still remain that Dr. Strauss and Dr. Loewe have succeeded in cultivating that virus, and have infected animals with it. The work is of importance also in that it helps prove the validity of the poliomyelitis work. Apparently, we will find that there is a number of filtrable viruses which show the same organism on microscopic examination. That they do not occur all over is evidenced by the fact that they are not present in the cerebro-spinal fluid in cases of poliomyelitis, but have been recovered from the spinal fluid in cases of epidemic encephalitis. For the present there is the greatest difficulty in deciding the nature of these organisms, except by animal inoculation. For proper classification, we will need new methods. It reminds me of the early work in bacteriology. When bacteriology was first begun, the organisms were grown in fluid media, and pure cultures could not, except by accident, be obtained. Later, solid media were introduced, and still later the brilliant mind of Theobald Smith increased our knowledge of differentiating these bacteria by means of studies in acid production. It seems to me that it is of the greatest importance to have men enter the field of bacteriology who have profound chemical knowledge.

As Dr. Strauss has pointed out, you can use the animal inoculations for differential diagnosis. Last summer I saw a woman who had been subjected to artificial induction of labor, because she was thought to be suffering from toxemia pregnancy. The clinical appearance of the case made me suspect that she was really suffering from epidemic encephalitis. I made washings of the nasopharynx, and they were injected into rabbits by Dr. Loewe. Typical lesions were produced in the animals.

DR. LOEWE: I wish to emphasize the fact that we cultivated the virus in solid media and selected isolated colonies. The colonies were then inoculated in fluid medium, and with such cultures positive results were obtained in animals.

ANEURYSM OF THE HEPATIC AND GASTRODUODENAL ARTERIES, WITH RUPTURE OF THE ANEURYSM INTO THE DUODENUM

HENRY R. MULLER, M.D.

The history in this case is brief, because the man, who was a postman, forty years old, was brought to the hospital one evening "in extremis." The only history which could be obtained was that about one month before, he had vomited a considerable quantity of blood. He had not been well since then, and had complained of weakness and frequent attacks of epigastric pain. Two days before his admission the patient began to have slight fever, it is said, with severe headache and abdominal pain. He vomited a considerable quantity of dark brown fluid which contained some bright red blood. On admission the patient's pulse was exceedingly small; he was cyanosed and very weak. During the night he was extremely restless, and he died about seven o'clock the next morning.

On admission his blood pressure was 105 systolic and 50 diastolic; temperature 100°, pulse 132, respiration 24.

Autopsy: The body was a well-developed and well-nourished male subject. The skin and mucous membranes were remarkably pale. There was no external evidence of syphilis. The bony frame was normal and showed no evidence of syphilis. Since the examination was restricted to the chest and abdomen, a good view of the base of the tongue could not be obtained, but so far as could be seen, there were no scars present. The penis was normal and a definite scar could not be made out. The testicles were larger than normal. Superficial lymph-nodes were not palpable, excepting in both groins, where they were slightly enlarged and indurated.

The *heart* was moderately enlarged, due to an hypertrophy of the left ventricle. The musculature showed no focal lesions except large opaque areas of degeneration in the tips of the papillary muscles in the left ventricle. Both coronaries showed early arteriosclerotic lesions and a few very doubtful lesions of syphilis were present in the upper thoracic and lower abdominal portions of the aorta.

The *lungs* were soft and fluffy, and showed a high grade of anemia. There were no focal lesions. The pulmonary vessels were normal and a search for syphilitic lesions yielded negative results.

The *spleen, adrenals* and *pancreas* were negative.

The *kidneys* appeared slightly larger than normal, their combined weight being 325 gm. The capsule was somewhat adherent. The cortex was slightly thickened, and the markings were indistinct, due largely to a high grade of anemia.

The *pelvis, ureters, bladder, seminal vesicles* and *prostate* presented nothing unusual.

The *liver,* pale yellow in color, presented no focal lesions. The bile ducts were patulous.

Of the *gastrointestinal tract,* the esophagus was normal. The stomach contained about one liter of blood-stained watery fluid. The mucosa of the duodenum was edematous, and a small circular ulcer, measuring 3 mm. across, was found on the posterior wall about 3 cm. from the pyloric ring. Behind the duodenum at this point was found an irregularly egg-shaped mass about 2 x 5 cm. The cavity in this mass communicated with the duodenum through the ulcer referred to above, and upon dissection proved to be an aneurysm of the hepatic branch of the cœliac axis, involving also the gastroduodenal branch arising from the hepatic artery. The sac was lined with laminated blood clots.

The remainder of the gastrointestinal tract presented nothing unusual apart from a hyperplasia of the solitary follicles of the colon, and the presence of a large amount of altered blood, particularly in the large gut and the lower ileum.

Microscopic Examination: Sections of the wall of the aneurysm showed practically an entire absence of elastic tissue fibers, the wall of the sac being made up almost completely of hyalin connective tissue. One section showed a small calcified plaque in the wall, and focal collections of lymphocytes around the blood vessels of the adventitia, and small collections of lymphocytes and large brownish pigment-bearing cells in the wall of the sac.

A section through one of the slight scar-like depressions of the aorta, suspicious of being syphilitic in the gross, showed no loss of elastic fibers nor any other signs of syphilis. There was only thickening and atheroma of the intima.

Sections of the wall of the aneurysm stained by Levaditi's method for spirochetes failed to show any such organisms.

A CASE OF SARCOMA OF THE LUNG

A. V. ST. GEORGE, M.D.

(From the Pathological Laboratories, Bellevue Hospital, Dr. Douglas Symmers, Director)

Primary tumors of the lung occur so infrequently that every case is well worth reporting. When the tumor is a primary sarcoma, it comes almost into the category of medical curiosities. Adler (1) was able to find only ninety cases in the literature, but many of these lack sufficient evidence to make his report entirely trustworthy. A case was reported in the *Medical Clinics of North America* (2), but the description is not quite clear as to the origin of the tumor. One or two other cases have been reported in this country during the past three years.

The patient was a man, age 52, who was admitted to Bellevue Hospital on the service of Dr. Nammack, whom I desire to thank for permission to abstract this case, on December 9th. He died December 26, 1919. The patient stated that he had a cough every winter for many years and expectorated a great deal during these periods. He had been feeling bad for a week, but did not stop work until three days previous to admission. He was suffering from extreme shortness of breath, was very weak and his temperature was high.

Physical examination showed a poorly nourished white male. The pupils were equal, reacted to light; no nystagmus; the scleræ were clear and the conjunctivæ normal. The mucous membrane of the mouth was slightly congested, the tongue covered and dry, and the tonsils slightly enlarged. There was no rigidity of the neck; the anterior and posterior cervicals were enlarged. The heart was displaced to the right of the mid-sternal line. Lungs showed flatness on left side from second interspace downward, anteriorly, and extending into the axilla as high as the second rib, and as far back as the mid-axillary line. Over this the vocal fremitus was absent. The dullness also extended to the posterior axillary line in the fifth interspace. The rest of the physical examination was negative.

December 13, 1919 (note by Dr. Nammack): The patient looked chronically ill, markedly emaciated, anemic and very irritable. The heart was displaced to the right so that the right border was two and a half inches to the right of the mid-sternal line. The apex seemed to be under the lower part of the sternum. The maximum impulse was in the fifth space, one inch to the right of the mid-sternal line. The left border of the heart could not be elicited. A systolic murmur was heard all over the right chest anteriorly. Over the second space on the left side there was a short to-and-fro murmur, probably pleuro-pericardial. The right lung was resonant all over and there were harsh vesicular breath sounds. The left lung was resonant in the posterior and anterior portions, from the apex to the second space. The breath sounds on this side also were harsh and vesicular. A few subcrepitant râles were heard at the base, anteriorly, from the second space down, and as far back as the posterior axillary line there was absolute flatness and absence of breath sounds. The veins of the abdomen were distended. The patient held himself rigid so that he could not be examined satisfactorily. The axillary, epitrochlear and inguinal lymph nodes were slightly enlarged. The knee jerk reflexes were hyperactive. Blood pressure: Right—95/45; left—95/50. Impression: Tumor of lung (primary), possibly Hodgkin's disease. The patient was running septic temperature.

December 16, 1919: Blood Wasserman negative.

December 18, 1919: Patient was running septic temperature with one or two chills every day. Blood culture was positive for *streptococcus viridans.*

December 20, 1919: Exploratory thoracentesis showed no fluid. Rectal examination was negative except for prostate being somewhat firm.

December 23, 1919: Roentgen-ray examination. The left pulmonic field was very small, due to complete obliteration of the illumination of the lower three fourths. The upper boundary of this area of illumination was convex and located at about the level of the second rib anteriorly. The lower boundary was located at the tenth rib posteriorly. There was obliteration of the illumination of the left costophrenic sinus. There was a small illuminated area between the left costophrenic sinus and the lower portion of the non-illuminated area. There was retraction of the trachea into the left thorax, and slight deviation of the heart to the right. The findings suggested the presence of a mass in the left lung associated with small pleural effusion. Diagnosis: Tumor of the lung.

The relatively sudden onset of the symptoms and the rapidly fatal course of the disease was of clinical interest in this case, and was also noted in several of the other cases reported. In this instance, the streptococcus viridans sepsis undoubtedly influenced the rapid termination.

Postmortem Record: The body was that of a white male, 52 years old, five feet, ten inches in height and weighing about 125 pounds. The external configuration of the body was normal, except for a marked generalized icterus and a small recent decubitus over the sacrum. Rigor mortis was complete. Postmortem hypostasis was present in the dependent portions of the body. The hair everywhere was normally developed and distributed. The lymph nodes in the left axilla were palpable. The scalp was clean and covered with gray hair. The pupils were equal, regular and in mid-dilatation. The scleræ were icteric. There was one petechial spot in the lower conjunctiva of the right eye. The nose and ears externally were negative. The teeth were in fairly good condition. The lips were dry and excoriated. The thorax was symmetrical. The abdomen was not prominent. The external genitalia were negative. There was a pendulous fibroma, about the size of a pigeon's egg, on the posterior aspect of the right thigh. The subcutaneous fat was poorly developed. The abdomen was dry and there were no adhesions. The liver extended 17 cm. below the free costal margin in the mid-axillary line. The diaphragm reached the seventh rib on the right, the fifth space on the left. The appendix was small and thickened and bound down by numerous adhesions to the posterior wall of the abdomen.

Chest. On opening the thoracic cavity, the heart was displaced to the right and downward so that fully 8 cm. of the precordial area was to the right of the median line. The thymus was not recognizable as glandular tissue and was replaced by numerous fibrous adhesions between the lungs, mediastinum and the precordial area. The left pleural cavity was practically obliterated by many firm and some easily destroyed adhesions throughout the entire extent except near the apex. The cavity contained approximately 20 c.c. of fluid. The right pleural cavity contained similar adhesions which were easily destroyed. The pericardial sac contained about 40 c.c. of yellowish purulent fluid. The visceral and parietal portions of the pericardium had a dull, reddish, glazed appearance on which there was some fibrinous deposit.

Heart. The heart was large, weighing 400 gm. The epicardium was of a dull red color as described. The muscle in the left heart was hypertrophied. On section, it was fairly firm, reddish brown in color, and there were numerous fine whitish striations, some of them very prominent. The endocardium was smooth but opaque in the left auricle and somewhat opaque in the left ventricle. The valves on the right side were normal. The foramen ovale was patent. The mitral valve was somewhat thickened, likewise the chordæ tendinæ, and there was slight retraction of their margins. On the aortic valves there were vegetations especially on the right posterior cusp where a large vegetation, roughly 75 x 100 mm., projected upward into the aorta. On the remainder of the cusps there were small verrucous vegetations. The cusps were fused for a distance of from 3 to 4 mm. Immediately behind the aortic valve there were hard, calcific atheromatous changes. The coronary vessels showed a few soft atheromata. The aorta showed atheromatous changes throughout its entire extent, more marked in the lowermost portion where there were calcific plaques. The pulmonary artery was normal.

Lungs. The left lung weighed 2285 gm. The lower lobe was most prominent and of a stony hardness. Its position in the thorax caused it to compress the upper lobe considerably so that this portion of the lung was soft and practically without air. At the apex there were a few small, calcific nodules. The lower lobe was everywhere covered by dense fibrous adhesions and connective tissue. On section, the entire lobe was converted into a stony-hard, white tumor mass in which no definite structure could be ascertained except here and there localized areas which had a distinctly yellowish tinge (Fig. 1). A few small, caseous areas were also present in this situation. The tumor mass resembled carcinoma, was very firm and not markedly vascular. The bronchi on this side were considerably congested and compressed, but contained no fluid. The peribronchial lymph nodes were not enlarged.

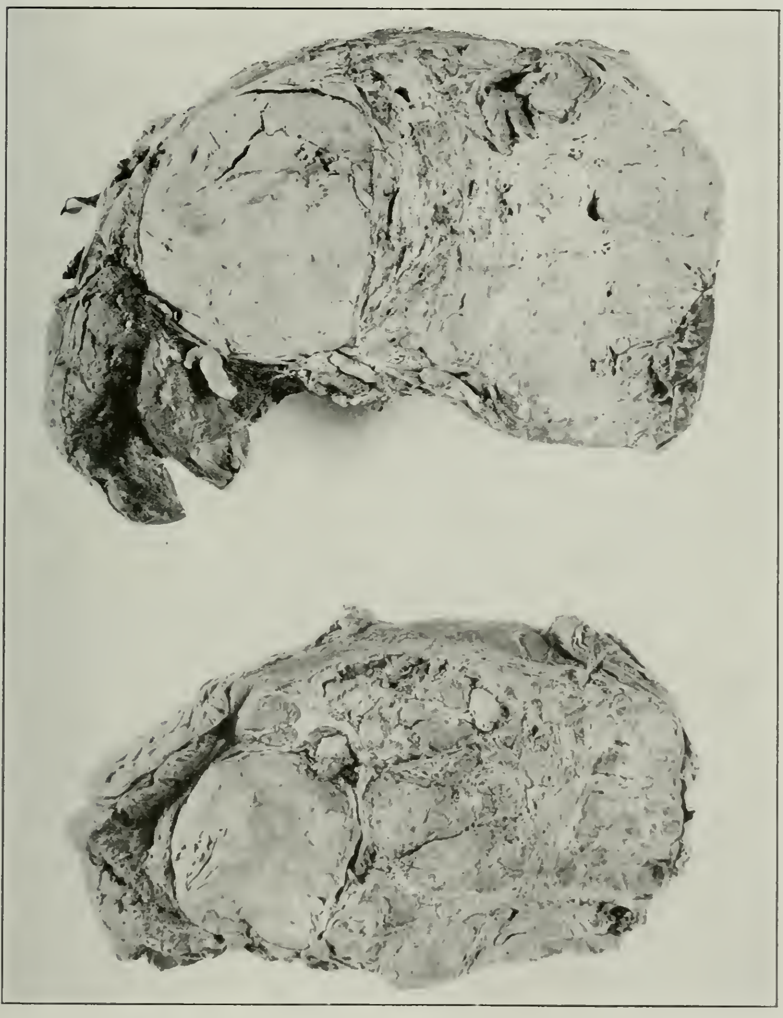


FIG. 1. Two cross sections of lung, showing primary sarcoma.

There was no definite point of origin of this tumor. The smaller bronchi in this lung were for the most part obliterated; the larger branches were dry and glazed.

The right lung was large and crepitated throughout. In the lower portion it was of a darker red color and firmer. On section and on palpation, there were a number of hard, circumscribed nodules which, on opening, were of a dull red color, somewhat paler in the center, the largest measuring not more than one and one half cm. in diameter, and the majority about the size of a pea. The lower lobe exuded a considerable amount of dark reddish, frothy blood. At the apex were two or three calcific nodules. The bronchi on the right side were congested and contained a moderate amount of pink, frothy fluid. The peribronchial lymph nodes were not enlarged. The mediastinal area showed no tumor formation.

Spleen: The spleen was large and weighed 655 gm. The capsule was not thickened. The organ was somewhat soft and friable. On section, it presented a dull red, grumous surface in which the lymphoid tissue was no longer distinguishable. There were two small accessory spleens in the mesentery near the lower pole. The splenic artery showed a few yellowish atheromata.

Liver: The liver was normal in size; the surface and border were smooth, and the organ was somewhat compressed in its antero-posterior diameter. On section, it presented a dull grayish color and exuded a slight amount of blood. There were no other lesions in the gross. The duct and vessels were patent. The gall-bladder wall was normal. The gall-bladder was distended with a considerable amount of dark green, sticky bile.

Pancreas: The pancreas was normal in size and normal on section. The lymph nodes at the head of the pancreas and in the region of the gall ducts were enlarged, pink in color and succulent, but without evidence of tumor growth.

Adrenals: The adrenals were normal in size. On section, they exuded a considerable amount of blood. Both adrenals contained whitish, irregular but sharply demarcated areas which were adenomata.

Kidneys: The kidneys were normal in size and imbedded in but little fat. The capsule stripped without much resistance, leaving a finely granular surface in which there were numerous whitish areas about 1 to 2 mm. in diameter (adenomata). On section, the cortex was somewhat narrowed and a considerable amount of fibrous tissue was present. In the cortex of the left kidney near the upper pole was a pale, somewhat oval shaped, sharply demarcated area, about 5 mm. in diameter, 1 to 1.5 cm. in length, and apparently a tumor metastasis. The pelvis and ureter of both kidneys were normal.

Bladder: The bladder was distended with about six ounces of clear urine, but there were no lesions in the gross.

Testes: The testes were normal in size and rather firm. The tubules pulled out readily.

Prostate: The prostate was normal in size. On section, it showed a very firm, somewhat cream colored, smooth surface.

Œsophagus: From its commencement to its termination in the stomach, it was normal.

Stomach: The stomach showed no marked lesions except slight congestion. The rugæ were prominent.

Intestines: The remainder of the large and small intestines showed no lesions in the gross.

Appendix: The appendix was much thickened and sclerotic and its lumen was considerably narrowed.

Tongue: The tongue was normal, as were also the larynx and trachea.

Thyroid: The thyroid was normal in the gross.

Brain: The scalp was removed without difficulty. The skull sawed through readily. On removing the calvarium, a considerable amount of pial fluid exuded from the cranial cavity and also considerable fluid was found in the pial tissue. Throughout the pia, especially on the convex surfaces of the cerebral lobes, there were irregular ecchymotic areas. The vessels at the base showed atheromatous changes. On section, the brain was otherwise normal.

Examination of the vertebræ and the pelvic bones, the head of the femur and the humerus, and some of the ribs showed no changes in the gross.

Note: Cultures from the spleen, at autopsy, showed *Streptococcus viridans.*

Anatomical Diagnosis:

Heart: Purulent pericarditis. Fibrous myocarditis, vegetative aortic endocarditis. Chronic mitral and aortic valvulitis. Patent foramen ovale.

Aorta: Atheroma.

Lungs: Apical tuberculosis, healed. Chronic adhesive pleuritis. Tumor of left lung with metastasis in right lung. Pulmonary congestion. Acute bronchitis.

Spleen: Acute splenic tumor. Accessory spleen.

Liver: Chronic passive congestion.

Kidneys: Chronic nephritis. Tumor metastasis. Adenomata.

Adrenals: Congestion. Adenomata.

Prostate: Adenomatous hyperplasia.

Appendix: Chronic appendicitis.

Brain: Pial œdema. Sclerosis of basal vessels.

General: Arterio-sclerosis. Icterus. Septicæmia, *Streptococcus viridans.*

Microscopic Examination: Microscopically, the primary tumor and the metastases in the right lung showed large, round sarcoma cells with a distinct perivascular and alveolar arrangement, forming the so-called alveolar sarcoma of the lung, similar cases of which have been described by Adami, McDonnell and others. Microscopic sections of the other tissues showed nothing remarkable. The metastatic foci everywhere had the same histological characteristics as the original tumor.

It is appreciated that the lesion primary sarcoma of the lung has often been questioned for many good and valid reasons. On the other hand, after as complete a search as we were able or permitted to make, no other site of origin was found. In this individual, as in other reported cases, the nature of the tissue from which the tumor sprang remains obscure.

References

1. Isaac Adler. Primary Malignant Growths of the Lungs and Bronchi, Longmans, Green & Co., New York, 1912.
2. *Medical Clinics of North America*, Vol. 2, p. 1145.

Discussion:

Dr. Pappenheimer: We have recently had two cases of mediastinal sarcoma at the Presbyterian Hospital, occurring within a few days of each other. In both of these the lung was extensively involved, and may have been the primary site of the tumor. They differed from Dr. St. George's case in the more extensive involvement of the mediastinal lymph nodes, and the possibility of their being lymphosarcomata was of course obvious. Histologically, however, neither of these tumors has the appearance of the ordinary lymphosarcoma, the cells being much larger in size and more polymorphous than is usual in lymphosarcoma. One of these tumors involved the upper part of the lung; the other grew from the hilus along the peribronchial and perivascular tissue, causing great thickening of the bronchi and blood vessels.

A CASE OF ACUTE YELLOW ATROPHY, WITH COMPENSATORY CHANGES IN THE LIVER

ELI MOSCHCOWITZ, M.D.

Cases of acute yellow atrophy are not so infrequent that they need be reported, but this specimen reveals some unusual and instructive features.

The patient was a woman 54 years old, admitted to Beth Israel Hospital on November 12. She gave a history of jaundice for nine months. A day or two before her admission to the hospital the jaundice increased, and increased progressively until her death four days later. The only other symptoms were weakness and epigastric distress. During the nine months previous to admission she was able to do her own work. She was irrational during her stay in the hospital. She became comatose toward the end.

Examination of the urine showed much albumin, casts, but no leucin or tyrosin. The Wassermann reaction was negative. The diagnosis of acute yellow atrophy was made by Dr. Barsky ante-mortem. The liver weighed 620 gm. (formalin). Unfortunately the organs showed considerable post-mortem necrosis. The capsule was wrinkled. On section the color was ochre red, scattered in which and lying close together were numerous irregular islets of yellow liver tissue. Microscopically, the ochre colored areas represented a fairly firm growth of new fibrillar connective tissue, which contained many round cells, remains of the capsules of Glisson, deeply bile stained epithelial cells and a large number of newly formed bile ducts. The yellow areas were islets of liver trabeculæ. These were well preserved, but the normal morphological unit structure of the liver lobule was absent. There was no central vein. The trabeculæ, especially in the central portion of these nodes, were broad, and contained sometimes three or more layers of cells. The nuclei were polymorphous and varied greatly in size and shape. An occasional mitotic figure may be seen.

These nodules may be interpreted as efforts on the part of the liver to compensate for the destruction of the liver parenchyma.

The first interesting feature is the unusually long history of duration of the illness. This is borne out in a measure by the histological changes in the organ. The large amount of new connective tissue can reasonably be interpreted as representing a duration of weeks or months rather than days.

The second interesting feature is the evidence of regeneration. This is shown not only in the development of new bile ducts but in hyperplasia of the liver trabeculæ. This liver represents, apparently, a stage just preceding that known as "nodular hyperplasia" of the liver.

Discussion:

Dr. Jobling: I should like to ask Dr. Moschcowitz if there was a history of any kind of intoxication, and also what was the occupation of the patient.

Dr. Moschcowitz: There was apparently no history of intoxication of any kind. The patient was a housewife.

Dr. Jobling: Had she been doing any sort of war work?

Dr. Moschcowitz: No, she lived on the East Side, and looked after her family, doing washing, etc. This case has made me wonder whether acute yellow atrophy is not really due to a progressive intoxication.

Dr. Jobling: What were the blood findings?

Dr. Moschcowitz: I think that the blood was not examined.

PATHOLOGICAL FINDINGS IN SEVENTEEN CASES OF PNEUMONIA DURING THE INFLUENZA EPIDEMIC OF JANUARY FEBRUARY, 1920

HENRY E. MELENEY, M.D., AND ALWIN M. PAPPENHEIMER, M.D.

The following is a summary of the pathological findings in the seventeen cases of pneumonia which came to autopsy at the Presbyterian Hospital, New York, between January 10 and February 7, 1920. The ages ranged between 20 and 70 years. There were eight males and nine females. The duration of the disease varied from 4 to 24 days, only three, however, being over 10 days in duration. Eight gave signs clinically interpreted as lobar consolidation. The other nine cases were described clinically as having bronchopneumonia or no definite signs of consolidation. Of 13 cases on which a leucocyte count was done, eight had 15,000 or more, one had 9,000, and four had less than 6,000. In the cases having a leucocytosis the pneumococcus was usually found to be the predominating organism at autopsy. The cases with a leucopenia all showed either no pneumococcus or a pneumococcus together with *B. influenzæ*.

At autopsy the cases presented a great variation in extent and type of lung involvement. In half the cases all five lobes were involved and in all these the confluent lobular type of pneumonia, usually associated with hemorrhagic edema, was the dominating picture. Three other cases each had four lobes involved and in two of these the confluent lobular type of consolidation predominated. In cases where only one lobe was involved consolidation was usually only of the lobar type. One case, associated with hemolytic streptococcus empyema, showed no consolidation.

All except one case of the series showed a pleurisy at autopsy. In one half of the cases one or both chest cavities contained purulent fluid. Usually this was not over 100 or 200 c.c. in amount. In two cases there had been great accumulation of pus, and on one of these a thoracotomy had been performed. Extensive empyema, then, cannot be considered a very prominent complication in this series. The only definite pulmonary abscess found in the whole series was in the unoperated case of empyema. The abscess was subpleural and on culture showed hemolytic streptococci and *B. influenzæ*. Bronchiectases were found grossly in three cases, and all of these were old lesions, judging by their microscopic appearance. In several other cases, however, microscopic examination showed small acute bronchiectases.

The gross and microscopic lesions of the various portions of the respiratory tract may be summarized as follows:

Larynx: This was examined in ten cases. It was usually normal or slightly congested. It showed ulceration in one case and slight edema in two cases.

Trachea and Primary Bronchi: These showed congestion in every case, varying from a mild degree to a very intense hemorrhagic condition which was present in about a third of the cases. There was gross ulceration only in one case. Microscopically most of the cases showed loss of epithelium with edema of the basement membrane, of the submucosa and of the peritracheal tissue.

Small Bronchi: A purulent or fibrino-purulent bronchitis was found in practically all cases. Three cases showed marked regeneration and metaplasia of the bronchial epithelium. These cases were all pneumonias (pleural) primarily of the influenza type. The rapidity with which metaplasia may take place is shown by the fact that in one of these cases the duration of the disease was only four days.

Infundibula and Alveoli: The exudate here varied not only in different cases but in different portions of the same lobe. There were patches of frank hemorrhage in about two thirds of the cases, and in all these the confluent lobular type of pneumonia was predominant. Fibrin was rather less in amount than is usually seen in lobar pneumonia, but in this series the amount of fibrin seems to bear little or no relation to the type of pneumonia present. Most of the cases showed many polymorphonuclear leucocytes in the alveolar exudate, and it is interesting to note that in almost every instance where there was leucocytosis during life the alveolar exudate at autopsy contained many pus cells. In cases with no clinical leucocytosis, however, the alveolar exudate contained either few cells, or else those present were mostly mononuclears. Only two cases were exceptions to this rule. There was marked edema of the lungs in about two thirds of the cases, occurring mostly, of course, in the unconsolidated portions of the lungs. Changes in the alveolar walls were in general not extensive, except for extreme congestion which occurred in the large majority of cases. Hyaline necrosis of alveolar walls, so often described in influenza pneumonia, was present in but three cases, and was extensive in only one case, that which was in every other way the most typical case of influenza pneumonia in the series. Interstitial inflammation of the lung tissue was not marked in any case.

Blood Vessels: Thrombosis of the vessels of the lung was never noted grossly, but was found microscopically in four cases. There was no associated lesion of the vessel wall in these cases, but in three other cases focal infectious lesions of vessels were found, characterized by necrosis and infiltration with leucocytes. These vessels showed no thrombosis although the intima in places showed swelling and edema. This is an interesting lesion which deserves further study in cases of pneumonia associated with influenza.

Bacteriology: During life, blood cultures were made on seven cases. Six of these were sterile, the other one showing pneumococcus Type 1. Sputum examinations by mouse inoculation were done on nine cases, showing a pneumococcus in eight cases and a non-hemolytic streptococcus in one case. At autopsy cultures were made on about half of the cases from the lungs, small bronchi and trachea. In the lungs 75 per cent. of the cases cultured gave a pneumococcus, or else *B. influenzæ* with either a pneumococcus or a staphylococcus. From the small bronchi and trachea, cultures were usually identical, and were never pure cultures of a single organism. The striking point is, however, that *B. influenzæ* was the only organism which was found in these localities in every case cultured. Microscopic sections of all lungs, and wherever possible of trachea and primary bronchi also, were stained with Gram-Weigert stain for bacteria, using saffranin as a counter stain. Seventy-five per cent. of the sections of trachea or large bronchi showed organisms. When present they were always on the surface of the mucosa. Gram-positive cocci were always present, and in addition two showed Gram-negative bacilli morphologically similar to *B. influenzæ*. Besides those found on the surface, two cases showed Gram-positive diplococci and one case *B. influenzæ* in the submucosa and in the peribronchial areolar tissue. In one case the peribronchial lymphatics were distended with fluid containing pus cells and many Gram-positive diplococci, many of which were disintegrating, and most of which were intracellular. This was the only case in which any involvement of peritracheal or peribronchial lymphatics was seen microscopically. Winternitz[1] has recently demonstrated by injection of india ink and bacterial suspensions beneath the mucosa at the upper end of the trachea that there is a very rich network of lymphatics in the submucosa of the trachea which anastomoses freely at the hilus of the lung with the peribronchial lymphatics. With this in mind we searched particularly for evidence of extension of the bacterial infection by way of these lymphatics, but our observations in this small series of cases do not support this idea. In the small bronchi fifteen of the seventeen cases showed organisms in section. Gram-positive cocci were present in every case. One case showed in addition organisms of the typical morphology of *B. influenzæ*. In no case were the organisms found in the wall of a bronchus or in the peribronchial lymphatics.

In the lung itself bacteria were demonstrated microscopically in the alveolar exudate in eleven of the seventeen cases. In all of these Gram-positive cocci were present, and in addition two cases showed Gram-negative bacilli morphologically typical of *B. influenzæ*, one showed a Gram-positive bacillus and one a Gram-negative diplococcus. In six cases no organisms could be demonstrated microscopically in the alveoli. These were all cases from which *B. influenzæ*, with or without other organisms, had been cultured at autopsy from lungs or bronchi.

---

[1] Personal communication.

Summary

Without attempting to draw any sweeping conclusions from such a small number of cases, certain points seem sufficiently definite to mention.

1. Our cases seem to fall into four groups:

(*a*) Cases identical with those of the pandemic of 1918 (2 cases).

(*b*) Cases with some of the features of influenza pneumonia, but showing also a consolidation tending toward the lobar type (10 cases).

(*c*) Cases of lobar pneumonia identical with those occurring independently of the influenza epidemic (3 cases).

(*d*) Cases of marked involvement of the pleura, associated with the hemolytic streptococcus, with or without consolidation (2 cases).

2. In general we found a fairly close correspondence between cultural bacteriological findings and organisms demonstrated in sections. *B. influenzæ*, however, was found much more often culturally than in sections.

3. There was an interesting correspondence between the white blood count during life and the composition of the alveolar exudate microscopically.

Discussion:

Dr. Pappenheimer: I think in spite of the small number of cases it is quite clear that there is a much greater diversity in the general run of cases than in last year's pandemic. Dr. Symmers has published a paper which I presume most of you have seen, calling attention also to some of these differences in type. Dr. Symmers emphasizes two points, especially: one, the greater frequency of suppurative pleurisy in this year's cases as compared with the last epidemic, and secondly, the very frequent occurrence of suppurative focal lesions in the lung associated with pleurisy. Abscess was found in only one of our cases, but there was a higher proportion of pleural involvement than in last year's epidemic. Some of the cases were frank lobar pneumonias not different from those of previous years, and we had the impression that many of the cases showed many of the features characteristic of influenza, but complicated by a secondary typical lobar pneumonia.

Dr. MacNeal: Were the cranial sinuses examined in these cases?

Dr. Meleney: The head was not examined in all the cases, but it was examined in about half of them. In four instances there was an acute sphenoidal sinusitis. Occasionally there was congestion of the ethmoidal sinuses, but in no cases were the frontal sinuses, the maxillary sinuses or the middle ears involved.

Dr. MacNeal: Did you make cultures from the sphenoidal sinuses?

Dr. Meleney: Yes, and they corresponded fairly well with what was found in the bronchi. The influenza bacillus, pneumococcus, particularly of type IV, and occasionally other pneumococci, were recovered. There were usually at least two or three types of organisms in the sinuses, and the question was raised at the time by Dr. Humphreys, who was doing the culturing, whether, particularly in the sphenoidal sinuses, there was a possibility that it might be just a terminal involvement.

Dr. Cecil: In experimental influenzal pneumonia in monkeys we found the sinuses in a large number of cases and usually the antrum, and very frequently both sides, filled with pus, and we recovered the influenza bacillus from the sinuses. Our cultures were not always pure. In some cases they were mixed with other common bacteria of the nose and throat.

Dr. Wheeler: I would like to inquire the methods used in isolating the influenza bacillus, and also the methods for staining it in sections.

Dr. Meleney: The isolation of the organisms at autopsy was done by Dr. Humphreys, and I am pretty sure that he used as a criterion of the influenza bacillus a Gram-negative bacillus of a definite morphology which was hemoglobinophilic. I think he used sodium oleate plates, but these were simply to inhibit other organisms, rather than to identify the bacillus itself. In the section we used a modification of the Gram-Weigert stain, using safranin as a counterstain, which differentiates quite beautifully.

Dr. Kline: Were there any discrete peribronchial lesions observed in the present epidemic??

Dr. Meleney: In making out our summary that was one point that we particularly looked for, and there was not a single case of purely peribronchial pneumonia. They were all either lobar, or what I believe you call confluent lobular, or hemorrhagic lesions.

Dr. Rohdenburg: I would like to say that I was much surprised last fall when reading a series of medical lectures given by Graves (famous because of his description of exophthalmic goiter), and published in America in 1815, by Graves and Gebhardt, to see that he described an epidemic occurring in Dublin. He stated that influenza has been common for some two hundred years. His description of the gross pathology in three successive years, the ordinary mild grippe, the severe pandemic form as observed last year, and the variation from the pandemic form as observed this year, might easily have been written in the present year, with the addition of the label "from such and such a laboratory." It is "up to the minute" except for the bacteriology.

THE PATHOLOGY OF EXPERIMENTAL PNEUMONIA[1]

RUSSELL L. CECIL, M.D.

The experiments described to-night were carried out on monkeys at the Army Medical School in collaboration with Dr. Francis Blake. The primary problem was to differentiate the pathology of the various types of pneumonia, that is, of pneumococcus, streptococcus, and bacillus influenzæ pneumonia. At least two, and sometimes all three of these organisms were often found associated in the pneumonias seen in the Army, especially during the influenza epidemic. It therefore seemed very desirable to clear up some of the problems in the pathology of the disease by trying to produce lesions with the organisms in pure culture experimentally. The method of inoculating the monkeys was to inject the bacteria directly into the trachea with a hypodermic syringe, the neck having been shaved and painted with iodine.

The pneumococcus strain used in most of the experiments was a pneumococcus type 1. The streptococcus was a strain of highly virulent streptococcus hemolyticus, while the influenza bacillus was a strain isolated from a fatal case of influenza. Its virulence for monkeys was increased by passage through other monkeys. The dosage used with the pneumococcus was small, a lobar pneumonia similar in every respect to lobar pneumonia in man being produced by doses as small as one-millionth c.c. of a broth culture. Increasing the dosage induced a type of infection in which the disease ran a more rapid course and death usually occurred. A dose of one-thousandth c.c. of pneumococcus type 1 always killed. With the *streptococcus hemolyticus* much larger doses than those used with pneumococci were necessary in order to produce fatal results. Apparently the invasive power of the streptococcus was not as great for monkeys as was that of the pneumococcus, and it was only after we had reduced the resistance of the monkey by "gassing" that we rendered the animals susceptible to the streptococcus.

---

[1] For a more complete discussion of this see Cecil, Russell L., and Blake, Francis G., *Jour. Exper. Med.*, 1920, xxxi, 403, 445.

In the experimental pneumococcus pneumonia of monkeys there is massive consolidation of entire lobes, similar in all respects to that observed in human lobar pneumonia, and microscopical sections show the alveoli filled with leucocytes and fibrin. Monkeys killed in the early stage of pneumonia showed the consolidation to take place about the root of the lung; that is, infection seemed to start about the larger vessels at the root and then spread throughout the rest of the lobe. This idea may not be accepted by all pathologists. Dr. Howard Mason once showed that pneumonia in children often appeared to start at the periphery of the lobe. In our experiments on monkeys however we have never been able to demonstrate an infection beginning at the periphery of the lobe. Microscopical examination shows that the pneumococcus spreads through the alveolar walls by way of the lymphatics, and the bacteria can be demonstrated in the tissues before any cellular reaction has occurred in the alveolus.

In monkeys with experimental streptococcus pneumonia the histogenesis is similar to that of pneumococcus pneumonia, but the cellular reaction is different. Engorgement and hemorrhage are more marked and small abscesses are frequently seen. Pneumonia of this type is usually complicated by empyema.

In experimental influenza and *B. influenzæ* pneumonia we have an entirely different set of lesions. Starting with acute rhinitis and sinusitis, the infection travels downward, producing first a tracheo-bronchitis and then in many cases extending on down into the lung, exciting a bronchiolitis, peribronchiolitis and broncho pneumonia. Pus is found in the bronchioles; there is infiltration of leucocytes about the bronchioles and cellular exudate in the adjacent alveolar walls. A few leucocytes are also found in the alveoli, but the latter more frequently contain serum and blood. There is engorgement and hemorrhage everywhere. The influenza bacilli are found chiefly in the bronchioles. In the latter stages of the disease emphysema and bronchiectasis can be demonstrated. The picture, in brief, is that of *B. influenzæ* pneumonia in man. Hyperplasia of the thymus was an almost constant finding with the *B. influenzæ* pneumonias. We interpreted this phenomenon as part of a general lymphatic hyperplasia of the cervical and thoracic lymph glands.

Discussion:

DR. KLINE: Did the lungs in the cases of pneumococcus pneumonia show any edema?

DR. CECIL: They nearly always showed some. In the gray stage the lungs were not edematous, but in the early stages of engorgement and red hepatization they were quite edematous.

DR. PAPPENHEIMER: Were the bronchi free from exudate?

DR. CECIL: They were nearly always filled with exudate.

DR. JOBLING: Did you try to produce the infection by spraying the throats with the cultures?

DR. CECIL: Yes, but without any effect at all with the pneumococcus or streptococcus. If you spray monkeys in the nose and throat with influenza bacilli they get a choryza and bronchitis, but we did not get any such effect with the pneumococcus or hemolytic streptococcus.

DR. PAPPENHEIMER: Were there inflammatory changes associated with the hyperplasia of the thymus?

DR. CECIL: Very little, if any. We found some leucocytes, but it seemed to be mostly a pure hyperplasia. There was not much infiltration; it was simply an enlargement of the entire gland.

DR. KLINE: Did all the monkeys with influenzal pneumonia show a peribronchial lesion, or did some of them show a lobular type?

DR. CECIL: In some there was a confluent lobular pneumonia. We would find areas where there would be a considerable infiltration, but we would never see a whole lobe consolidated.

DR. KLINE: In a series of 154 cases of pneumonia we saw twenty cases in which there was this type just described: a discrete peribronchial and peribronchiolar lesion.

DR. CECIL: It would be interesting to know the bacteriology in those cases.

DR. KLINE: Pneumococcus, *B. influenzæ*, *micrococcus catarrhalis*, etc., were found in about the same proportion as in the other types of pneumonia following influenza.

DR. CECIL: The most interesting feature of these experiments has to do with the bacillus influenzæ infections. I would like to know just how you gentlemen feel about these lesions—how they compare with what you have seen in human influenza-pneumonia. It is very rare of course to find the influenza bacillus in pure culture in human pneumonia, and therefore it is hard to compare it with the disease in monkeys, but I have studied very carefully the papers by Wolbach and MacCallum, both of whom have described the pathology of pure influenza bacillus pneumonia, and it seems to me that there is very little difference between their cases and the ones I have shown you to-night. We would naturally have every reason to expect that the injection of influenza bacilli into the lungs of a monkey would produce a type of lesion similar to that observed when this organism is found in man.

Dr. Kline: It is very interesting that Dr. Cecil produced lobar pneumonia in monkeys with one c.c. of culture injected intratracheally. In 1915, in association with Dr. Winternitz, rabbits were injected intratracheally and intrabronchially, and it was found that rabbits that were given five c.c. of pneumococci intratracheally developed no lesion in the lung, but that all animals given pneumococci intrabronchially developed lobar pneumonia. Dr. Winternitz produced lobar pneumonia and I could not, so experiments were done to find out why, and it was discovered that in rabbits there is a remarkable protective mechanism in the bronchi and trachea that gets rid of the pneumococci. Our experiments were carried out with catheters, and I believe Dr. Winternitz thinks that with injection by means of the needle the tissues of the neck are infected when the needle is drawn out, and it is possible that the organisms reach the lung through the lymphatics of the trachea and bronchi. The pictures that were shown on the screen of lobar pneumonia are not those which one sees in experimental pneumonia in rabbits. Such large doses of fluid, usually five, six, or seven c.c. filling the lobe, cause an exudate everywhere and a process more nearly resembling the lobar pneumonia one sees in man. We did not observe the gradual spread. It seems to me that in the pneumonia produced in monkeys by intratracheal injection the lungs show more mottling, that is, the process is more advanced in some portions and less so in others. I think that when the bacteria are introduced intrabronchially the process more nearly resembles that in the human being.

Dr. Pappenheimer: We are all interested in this question, and I think that we shall all agree that there are many resemblances between the type of pneumonia Dr. Cecil has produced and the type we have learned to call influenza pneumonia. These resemble each other especially as regards the hemorrhagic character of the lesions, the involvement of the bronchioles, and the tendency to bronchiectasis. There are wanting in Dr. Cecil's preparations certain features which perhaps as Dr. Cecil says may be caused by the admixture of other secondary organisms, but which do not accompany infections with these organisms alone, so that we have come to look upon them as more or less specific for the influenza type. One of these features is the hyaline necrosis of the infundibuli which almost all of the workers have described. Then the majority of Dr. Cecil's lesions has been pretty definitely peribronchial, more the type of pneumonia that MacCallum has described as a sequel to the post-measles pneumonia, and that I think is generally attributed to the *Streptococcus hemolyticus*. The influenza-pneumonias that we saw in human cases were only exceptionally limited to the bronchi. The striking thing about these pneumonias was their very great extent, not as complete consolidation, but as a diffuse hemorrhagic edema, more or less of the pseudo-lobar type. Dr. Cecil has not shown any of the later stages, and I would like to ask him if he has found in the later stages the extensive hyperplasia of epithelium from the bronchi into the neighboring alveoli which seems to be one of the striking features of the influenza pneumonias. I should like to ask also whether there was a possibility of spreading the infection from the site of inoculation along the deep lymphatics, and whether he studied the trachea of his animals, to determine this point.

Dr. Cecil: I was much interested in Dr. Kline's remarks, particularly in regard to infection taking place in the lymphatics about the trachea. I think we controlled that fairly well. We injected a series of three monkeys subcutaneously over the trachea with pneumococci to see if we could produce pneumonia by subcutaneous injection. We were never able to produce pneumonia in a healthy monkey by any method except direct intratracheal injection. We did a contact experiment with some monkeys in a cage, and we were able to produce contact pneumonia. Spraying the nose and throat failed. Subcutaneous and intravenous injections failed to produce any involvement of the lungs. If these monkeys had first had their lungs injured our results might have been different.

In answer to Dr. Pappenheimer's questions, we cut sections of the trachea in nearly all cases, and were never able to see any involvement of the wall of the trachea. In fact, there was usually little inflammation of any kind in the trachea. There was certainly no infiltration of the wall of the trachea, such as we see in human influenza cases, which have almost constantly an acute tracheitis. That is an interesting difference between the influenza infections and the pneumococcus infections. We were looking hard for hyaline necrosis in the alveoli, but we were not successful in finding it. I noticed in sections that Dr. MacCallum sent me that hyaline necrosis was absent in three cases, but it was present in Wolbach's cases. Perhaps I overemphasized the bronchiolitis in our cases, but I think the pictures of the gross specimen are sufficient evidence that we produced a good deal more than a bronchiolitis in these cases. There is an intense edema and hemorrhage, in some cases, especially in the early stages. Another striking thing was the absence of fibrin. We did not get any pleurisy in any of these cases.

CARCINOMA OF THE BRONCHUS WITH THROMBOSIS OF THE SUPERIOR VENA CAVA

RALPH G. STILLMAN, M.D.

(From the Department of Pathology of the New York Hospital)

Carcinoma of the bronchus is not an excessively rare condition but it is sufficiently infrequent to make worth while the mention of the cases that occur. In addition this case which I am presenting has certain features which make it interesting.

The patient was a Russian grave-digger, 38 years old. He was admitted to the Second Medical Division of the New York Hospital on February 11, 1920, complaining of a swollen throat and spitting of blood.

His family history is negative.

His past history contains little of interest. He had measles in childhood and malaria twelve years before admission. He had been accustomed to several beers and an occasional whiskey and five to six cigarettes daily. He denied venereal infection. He had been subject to chronic cough lasting two or three months at a time but had never had any hemoptysis prior to his present illness. About eighteen months before his admission he began to be a little short of breath on exertion.

His present illness dates from an attack of influenza in March, 1919, eleven months before admission. He had pneumonia at that time and was sick for four months, during which time he was never free from cough and hemoptysis. He went back to work after his recovery but was not free from symptoms and in December, 1919, was forced to stop work. The cough, hemoptysis and dyspnea had grown steadily worse since that time and during the two months before his admission to the hospital were quite severe. He never brought up more than a mouthful of blood at any one time and this was sometimes bright red and sometimes "black."

On admission he was seen to be slightly dyspneic and exhibited well-marked edema of the face, chest and upper extremities. Over the lungs the percussion note was dull throughout. The breath sounds were distinct. There were many sibilant and sonorous râles throughout both chests, with a suggestion of tubular breathing heard at the right of the sternum at the level of the third rib. The reflexes were normal. In the middle third of the right thigh on the postero-external aspect there was a hard mass, about 2 cm. in diameter which felt as if below the fat layer. There were many nodes palpable in the axillæ, some of them measuring as much as 15 to 20 mm. in diameter. The posterior cervical and the inguinal nodes were small but palpable.

His urine showed the presence of a small amount of albumin but no casts. The red cells numbered 3,500,000 and hemoglobin 60 per cent. The white cells were 10,600 and the polynuclears 86 per cent. Two Wassermann reactions were negative. His temperature was normal on admission but rose gradually and varied between 101° and 104° during the last ten days of life. X-ray plates made about ten days before death showed a large mediastinal shadow and signs of infiltration in the right upper lobe. A lymph node was removed from the right axilla but showed only a mild grade of chronic inflammation. He grew progressively worse but was not considered dangerously ill when suddenly one night he had a large hemorrhage from the lung and died.

Autopsy was done on February 26, fourteen hours after death. Only the important findings are given here. The head and arms appeared large in proportion to the rest of the body. There was well-marked edema of the subcutaneous tissues of the head and arms and of the trunk down to the level of the xiphoid cartilage. No edema was apparent below that level. Beneath the skin over the posterior surface of the right thigh was a small nodule which was very firm and movable, both beneath the skin and on the deeper structures.

The right pleural cavity was dry. The apex of the right lung in its posterior aspect was firmly fixed to the chest wall and was badly torn in the efforts to free it. When the tissue was torn a small amount of dark gray fluid escaped into the pleural cavity. After the removal of the lung, the tissue remaining presented as a thin layer of dark gray tissue whose surface was quite smooth and shining.

The contents of the thoracic cavity were removed *en masse*. The lungs were voluminous, the left was light gray and showed a moderate amount of compensatory emphysema. The right lung presented posteriorly, corresponding to the area of adhesion described above, a ragged cavity measuring about 7 x 9 cm. and situated in the posterior portion of the upper lobe. On opening the trachea it was found to contain a blood clot which filled about one third of its lumen and extended down into the bronchi. The right bronchus, at about 2 cm. from the bifurcation of the trachea, terminated abruptly at the margin of the above-mentioned cavity. This cavity was lined with ragged necrotic tissue and in its walls could be seen the eroded ends of several of the smaller bronchi. There were several blood clots adherent to the wall. One of the branches of the bronchus was opened beyond the cavity and traced down into the lower lobe. The lung in this region was thickly studded with round yellow nodules measuring 3 to 12 mm. in diameter. There was obviously a pneumonia in this portion of the lung but some of these nodules resembled greatly carcinomatous metastases.

At the bifurcation of the trachea was a lymph node about 4.5 cm. in diameter which was largely necrotic. There were several smaller nodes in this region.

The heart was rather small. In the pericardial cavity, at a point corresponding to the reflection of the pericardium and situated nearly at the level of the bifurcation of the trachea, there was a cauliflower-like mass, about 1 x 1.5 x 5 cm. which projected into the pericardial cavity. At one point this mass had grown directly into the lumen of the superior vena cava and appeared there as a small, irregular, firm, pale mass located about 4 cm. above the auricle. Immediately below this mass the lumen of the cava was constricted to a diameter of not more than 4 mm. Above this mass the cava was filled with a thrombus which was pale and firm below but dark red and soft above. This thrombus completely occluded the vessel.

The only metastases found in addition to those in the mediastinal nodes were in the kidneys, each of which contained several nodules of a typical carcinomatous appearance. The nodule in the thigh appeared to be entirely fibrous. The other organs showed nothing noteworthy.

Microscopic examination of the organs showed the lesion to be a carcinoma originating in the bronchus. Section of the right bronchus at the margin of the cavity showed very well the infiltration of the carcinomatous cells beyond the mucosa. The lesion in the lung proved to be a pneumonia with abscess formation. No neoplastic tissue could be found in the lung except in the immediate vicinity of the cavity. The lesions in the kidneys and the mass in the thigh both proved to be metastatic carcinomas. The tumor was of the cylindrical cell type as could be especially well seen in sections taken from the margin of the cavity in the lung. The greatest interest, perhaps, is found in the study of the metastases in the kidney and the subcutaneous nodules from the thigh. In the kidney, the cells are nearly all flattened or cuboidal and not infrequently resemble greatly the alveolar epithelial cells both in shape and in staining qualities. Further they are at times collected in areas that resemble the alveoli. Some of the cells are collected into whorls that bear some resemblance to pearls but which do not have keratinized centers. From a study of this section alone one would perhaps be justified in concluding that we were dealing here with a tumor having its origin in the alveolar epithelium.

On the other hand the nodule from the thigh shows almost exclusively cylindrical cells resembling those found in the bronchial epithelium and in some places the structure of the bronchus is fairly faithfully reproduced except that none of the cells seem to be ciliated. From a study of this section alone the conclusion would be inevitable that the tumor arose from the bronchial mucosa.

Practically all of the authors who discuss this subject have noted the tendency, especially of the cylindrical cell carcinomas of the bronchus, to show this great variation in the types of the cells, but it is rather interesting to see these two types displayed in two different places in such a striking manner. One may perhaps be permitted to speculate as to whether the consistence of the tissue had anything to do with the morphology of these cells for the squamous cells occurred in the soft tissue of the kidney while the cylindrical cells were found in the firm fibrous tissue of the subcutaneous nodule.

Discussion:

Dr. Kline: At the Montefiore Hospital in the course of over 375 autopsies we have had ten cases of carcinoma of the lung. It is interesting that our last case was very much like the one just presented, except that the tumor arose toward the root of the left lung and extended through the pericardial sac and grew right through the wall of the left auricle. The growth was covered over by an ordinary laminated clot. We have not as yet collected data concerning the nature of the cells making up the tumors, but my impression of the different types is that the most confusing of all, the squamous cell type, might arise from an epithelial growth over cavities formed at some previous time. In going over a number of cases of chronic pulmonary tuberculosis with healed and healing cavities we have seen a downgrowth of epithelium, apparently from the bronchial epithelium, over the cavities, that is, lining the cavities. This has been squamous in character, and we have felt that possibly some of the squamous celled carcinomata of the lung might arise in this way. We have also seen cylindrical cell carcinoma and in one of the cases the cells were very much like the alveolar epithelial cells. The distribution in this alveolar cell tumor was throughout the body of the lobe, not continuous with the bronchi.

Dr. Baehr: As a further contribution to the study of carcinoma of the lung, I should like to mention an interesting series of coincidences, if they are such, at the Mount Sinai Hospital. Amongst 4,000 autopsies we have three times encountered an association of primary carcinoma of the lung and chronic lymphatic leukemia. The last case occurred about a month ago. In all three cases the primary carcinoma of the lung was accidentally found at the autopsy table. Recently in reciting these experiences to Dr. Gideon Wells he remarked upon the association in mice of carcinoma of the lung and sometimes carcinoma of other organs with a chronic lymphatic leukemia, and his explanation of the association of the two was along the lines of heredity, that is, that the two conditions are sometimes inherited in the same strains.

Dr. Moschcowitz: I should like to ask Dr. Stillman if there was any evidence of dilatation of the superficial vessels.

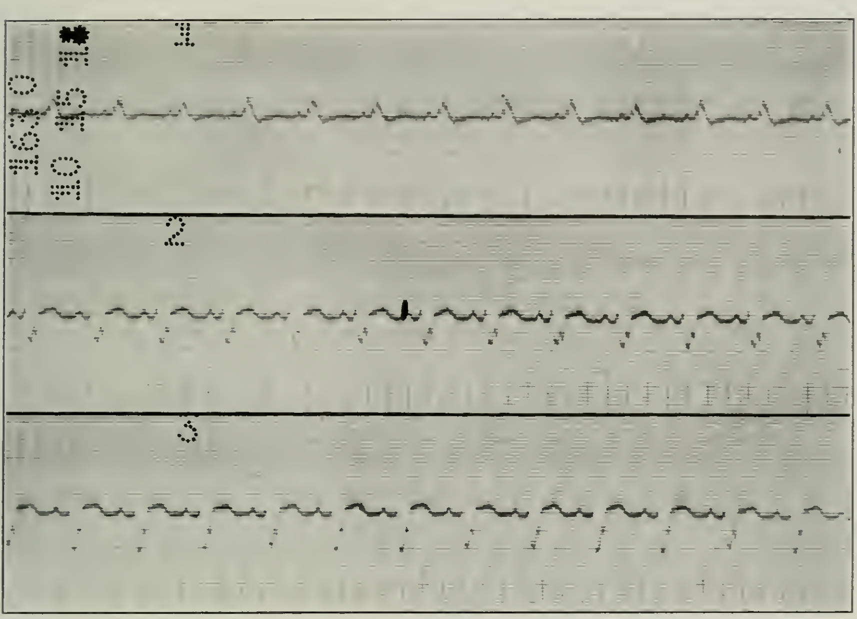
Dr. Stillman: No. There was so much edema that the superficial vessels could not be made out.

LOCALIZED CHANGES IN THE HEART MUSCLE AS DETERMINED TO BE IN THE RIGHT BUNDLE BRANCH BY THE ELECTROCARDIOGRAPH

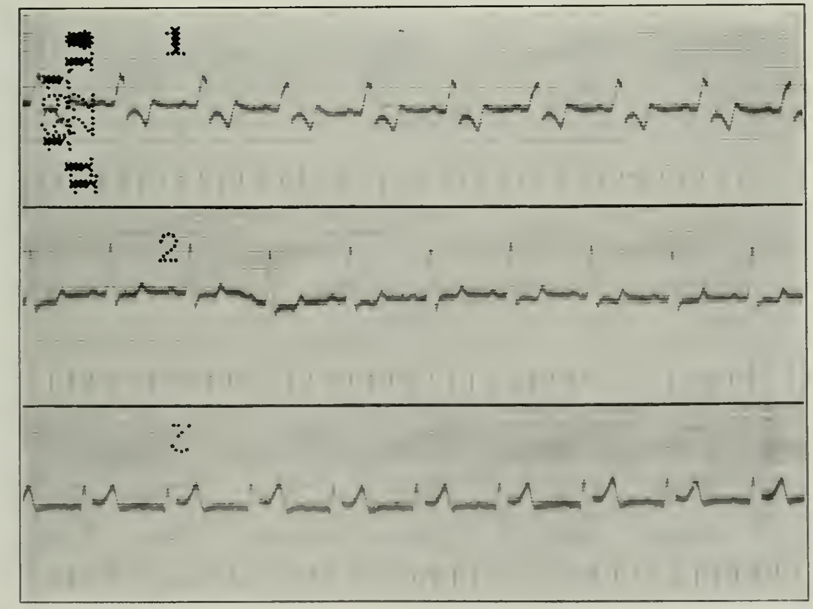
LOUIS FAUGERES BISHOP, A.M., M.D., SC.D., F.A.C.P.

(Clinical Professor of Heart and Circulatory Diseases, Fordham University School of Medicine, New York City, Physician to the Lincoln Hospital, New York)

The electrocardiograph is an autograph of the heart beat and as such has a large value in bridging the gap which a physician must cross in becoming personally acquainted with the cardiology of his patient. It is like handwriting, the effect of which is very striking in giving an impression of the personality of the writer. So there is a value to the electrocardiograph that is not at present reducible to scientific terms. This represents the extreme and indefinable value of the method. On the other hand, the most striking example of definite, demonstrable, scientific



1 L. H. B. D.



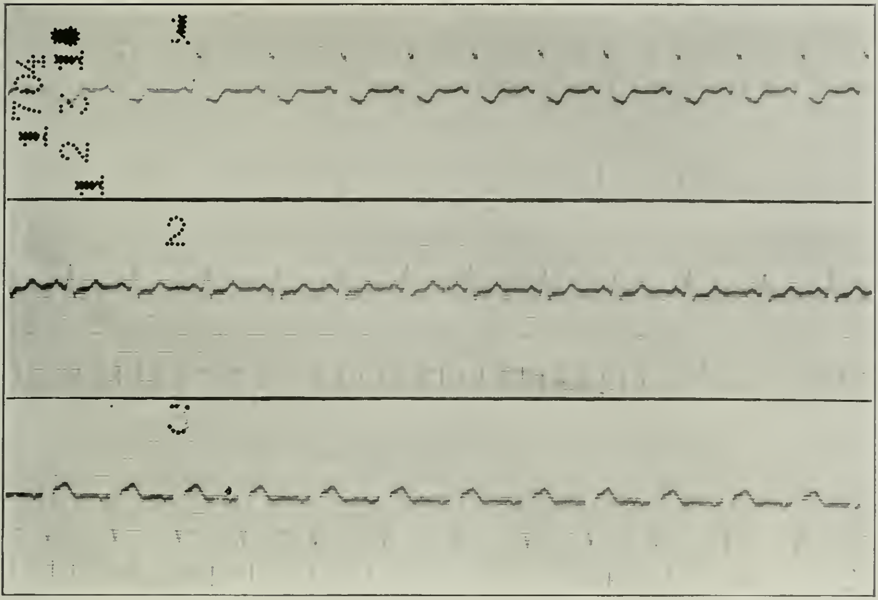
2 L. H. M. L.

value when we have excepted the recognition of the six cardial irregularities is found in those people who have suffered a definite, localized damage to one of the branches of the bundle of His. This very often is the direct result of rupture, thrombosis or embolism of a vessel of the heart, the occurrence of which is frequently revealed in the history of the person by the story of an attack characterized by severe cardiac pain of long duration with very marked heart failure from which the person gradually recovered. As in the corresponding cerebral event, the lesion may be, and often is, thrombosis, sometimes it is an embolism and occasionally a rupture.

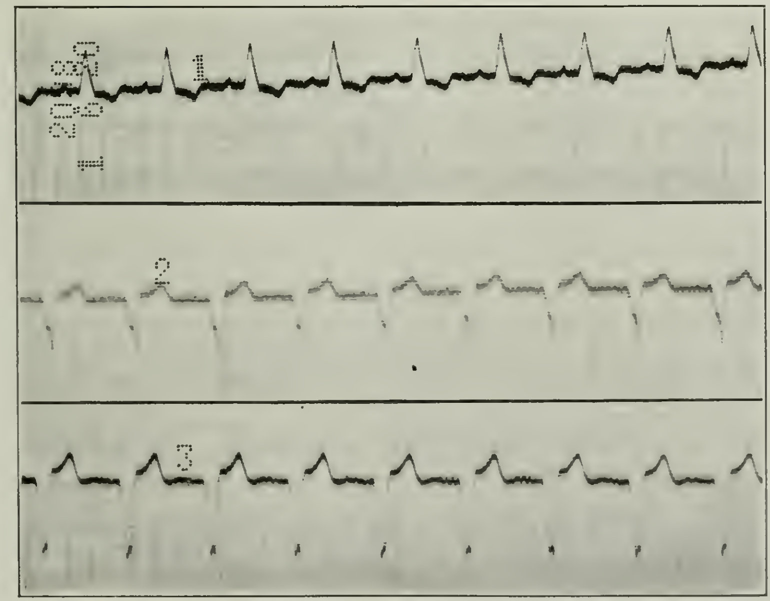
I am showing you about twenty examples of electrocardiographic records which occurred in the last 700 people as examined in my office. This may give you some idea of the relative frequency of this condition, in that group of people whose cardiac condition is of sufficient importance for them to seek a complete technical examination. It also shows that cardiac disease is usually allowed to advance to a high degree of development before people receive the benefit of a close analysis of their heart condition.

In this group of twenty people who were suffering from a disease which involved the terminal branches of the bundle of His all but three were over fifty years of age, and all but four were males. The duration of the disease previous to the time when the patient came to my office was nearly always considerable. In only four patients was it less than a year.

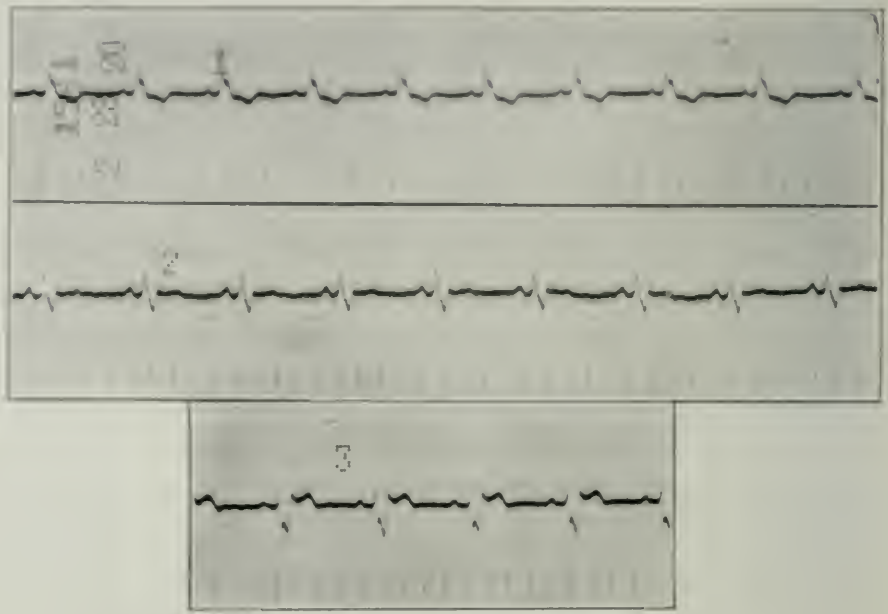
The prominent symptoms of which these people complained were precordial pain, dyspnœa and palpitation. Pain of some sort was present in all but two of these cases and was sharp and severe in eleven. Sometimes it was described as a sense of soreness or a dull pain or a feeling of oppression. The situation of the pain is variable, but nearly always includes the precordium at least in part. In five of the patients the first symptom of disease was pain, while in four the first symptom was shortness of breath In the remainder of this group the symptoms had rather an insidious onset, and it was difficult for them to say of what they first complained.



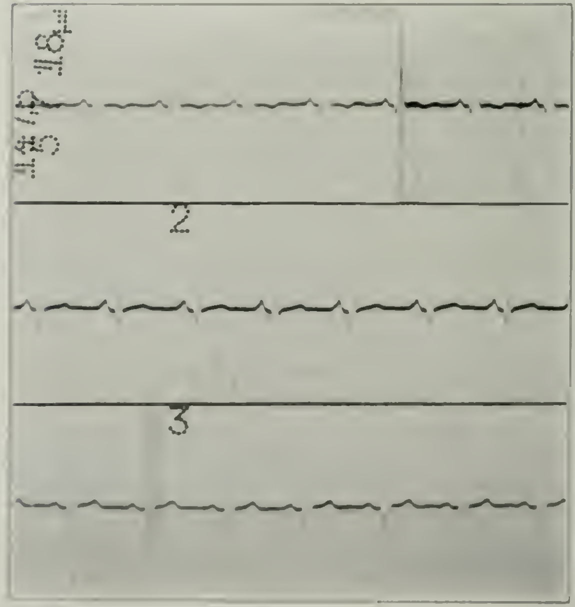
3 L. O. D. I.



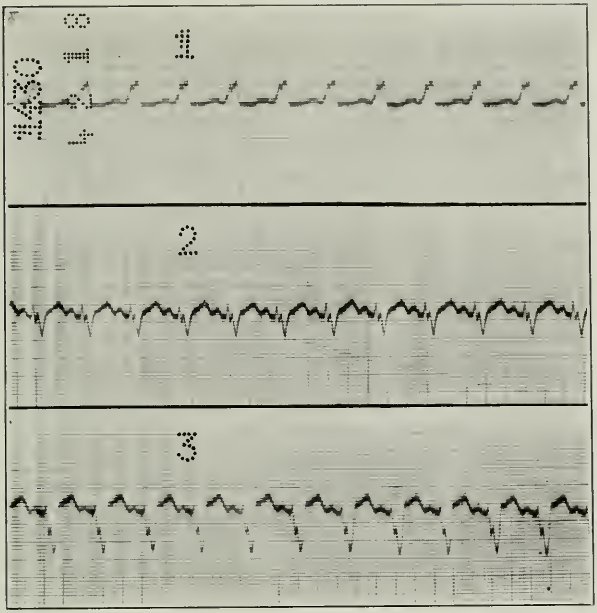
4 F. T. M. P.



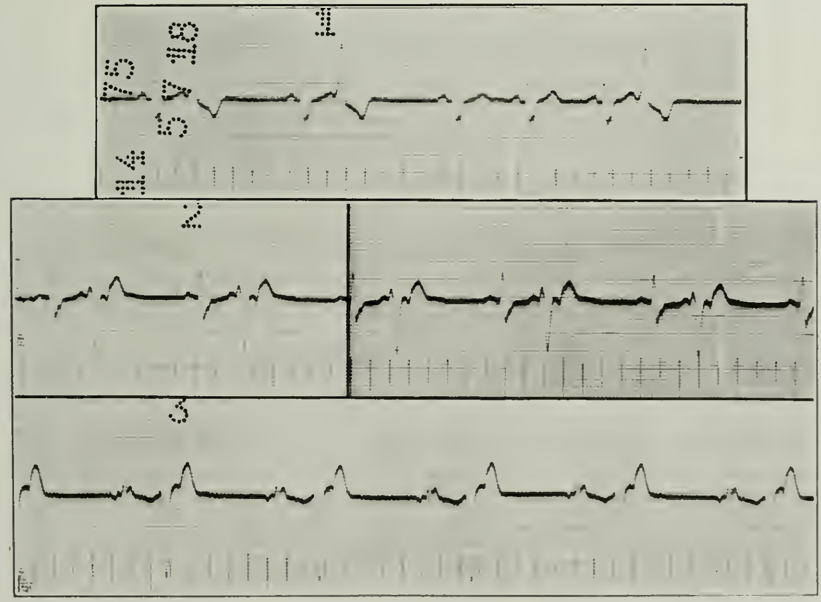
5 L. S. P. L.



6 L. I O. H.



7 L. I. B. D.



8 L. I. O. S.

Although dyspnœa is usually a prominent symptom, there was one of these people in whom it was not present and another one in whom it was only noticed at night when it came on in attacks.

Palpitation appears in attacks on exertion. It was present in eight of these persons. When present it is usually a distressing and prominent symptom.

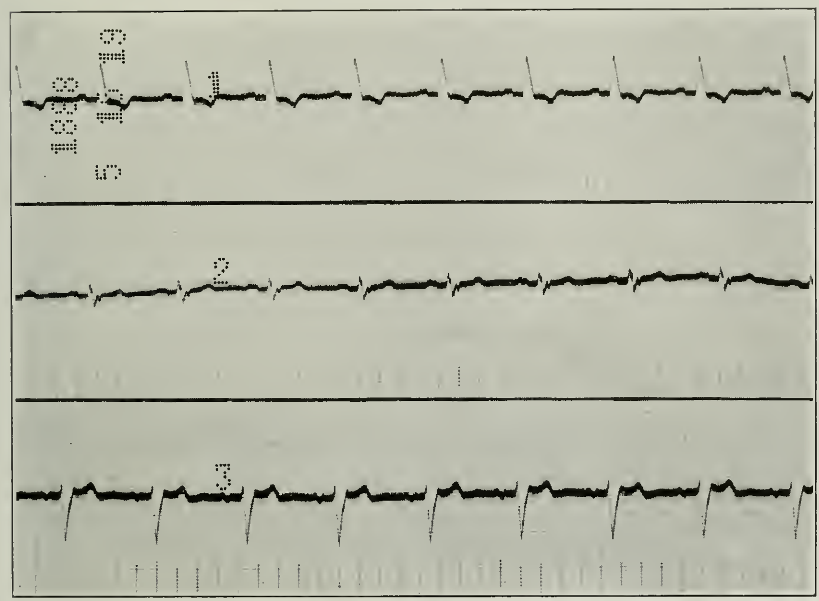
Œdema, strangely enough for a condition which is usually considered so serious, did not occur very frequently and when present was not marked, except in one person. Fifteen of these people did not show it.

The weakness of the heart tends to cause a congestion of the lungs which is manifested in cough and this was present in about half of these people. It was not severe, but was very persistent.

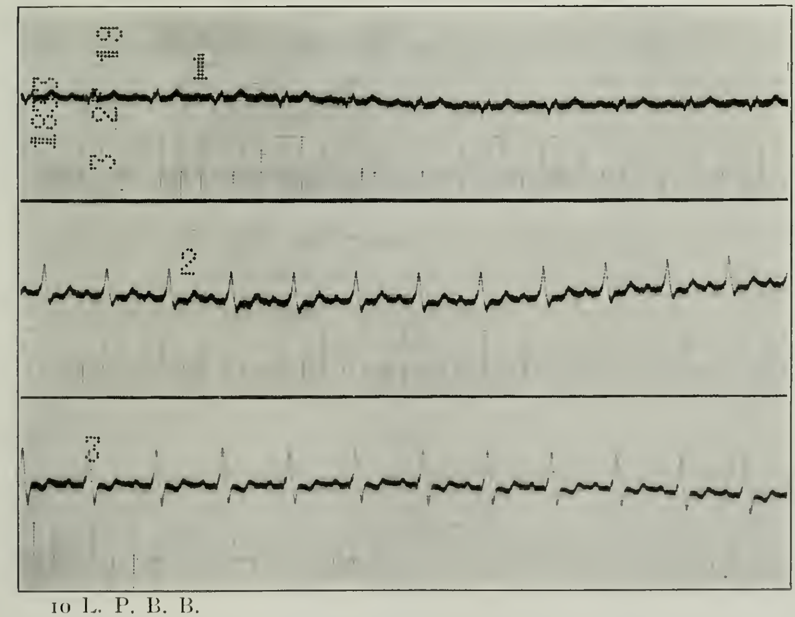
When these people were examined, the most evident thing about them was their age. In going over their records, it is also evident that the majority of them had increased blood pressure, although it is true that some did not show this. Blood pressures in this series were observed as high as 220 mm. for the systolic and twelve of these people gave figures for the systolic which might be considered above normal.

The heart rate was usually not rapid when they came for examination, being over 90 in only six patients, and in only one person was it very rapid, being 120 in that case.

The electrocardiographic record shows the changes which are considered as typical of an obstruction in one of the branches of the bundle of His, in all of these people. The ventricular waves have the large notched Q, R, S group with increased width and the large T wave in the opposite direction, which is typical. All but three of them have the Q, R, S deflection chiefly upward in lead 1 and downward in lead 3, so that the lesion may be said to be in the right branch of the bundle. The other three records probably have a lesion in the left branch of the bundle. One of the records shows the person had auricular fibrillation, but in all the others the normal rhythm is in force. Three cases showed premature ventricular beats and one showed a prolonged conduction from between the auricles and ventricles.



9 L. P. P. P.



10 L. P. B. B.

The x-ray pictures which were taken of these people by the teleoroentgengraphic method show that four of these people did not have an enlarged heart. Five of them had extremely large hearts and in the remainder there was a moderate enlargement.

It is a very interesting finding that eleven of these patients were considered to have normal valves and in four of them both the aortic and mitral valves were diseased, while in the remainder only one valve was affected.

Eight people showed systolic murmurs at the apex which were not considered to indicate valvular disease.

In our attempts to treat these people, we have been able to observe the response to digitalis in sixteen of the twenty persons and have found that in seven of them it had an extremely beneficial effect. Four were only moderately benefited by digitalis and in five the response was poor.

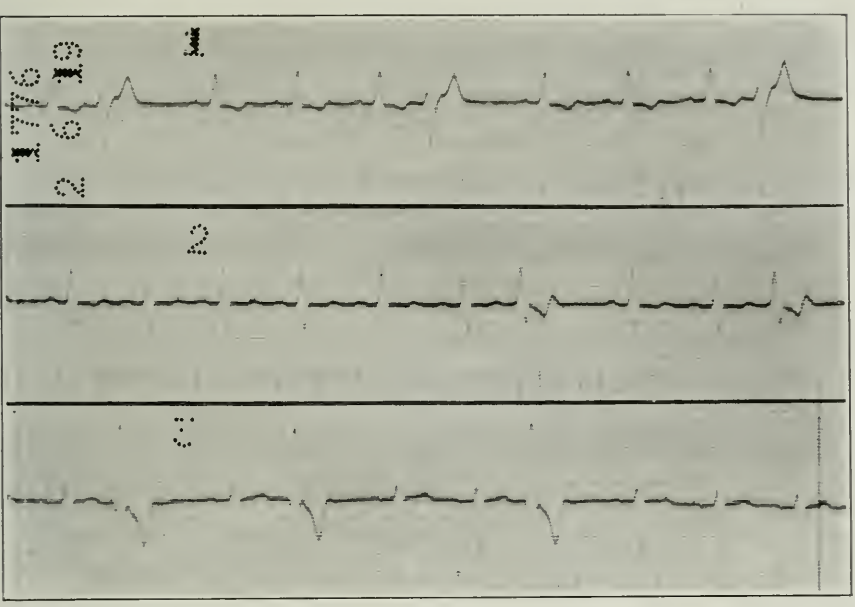
It has been said that all of these people are persons who are well advanced in years and so it is not surprising that our clinical diagnosis, after having reviewed all of the findings, should be arteriosclerosis in eight of these people, cardial-sclerosis in one other, and angina pectoris in still another. This indicates that these people were suffering chiefly from a condition which goes with age and is not especially brought on by any acute disease.

Five of them were left to go with the diagnosis of myocardial degeneration, while four were believed to have primary valvular disease. In the one remaining person, our diagnosis was cardiac dilation.

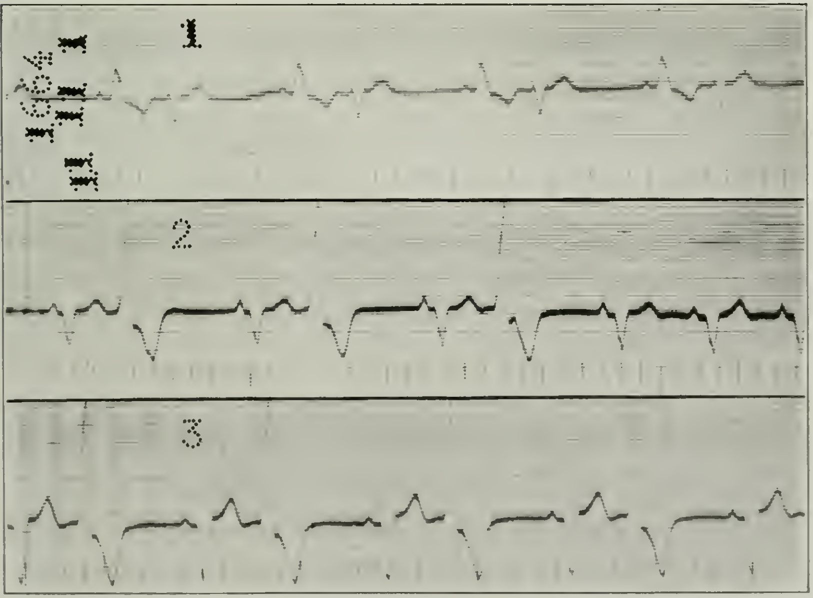
Several of these people, and curiously not those who showed the most striking electrocardiographic pictures, are still under occasional observation and are able to pursue their vocations in a manner that is equal to the average of their age.

All these observations were made in private practice, and bears out the belief expressed by at least one of the greatest heart specialists in the world, that the most fruitful field for the study of cardiology is found in private practice.

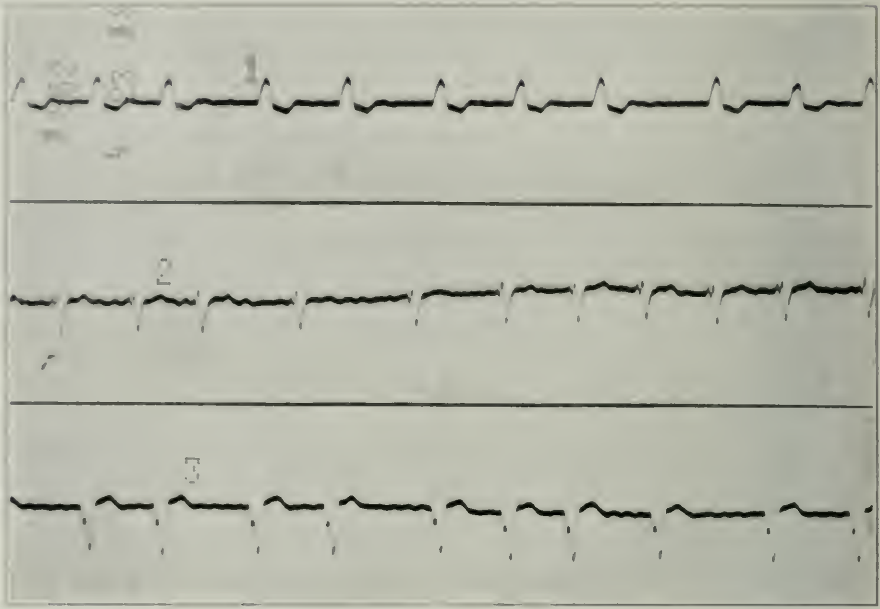
The general condition of the heart must be very good indeed when it can survive and make so good a comparative recovery



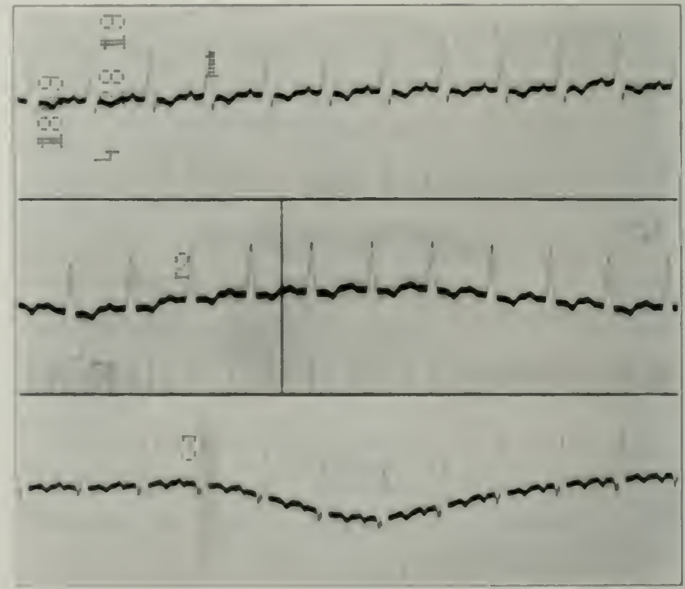
11 L. O. O. H.



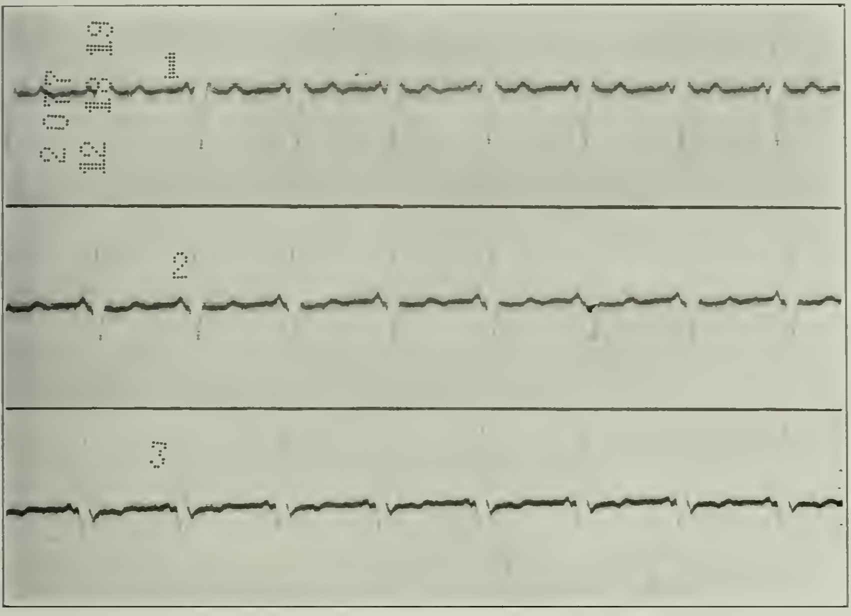
12 L. H. H. I.



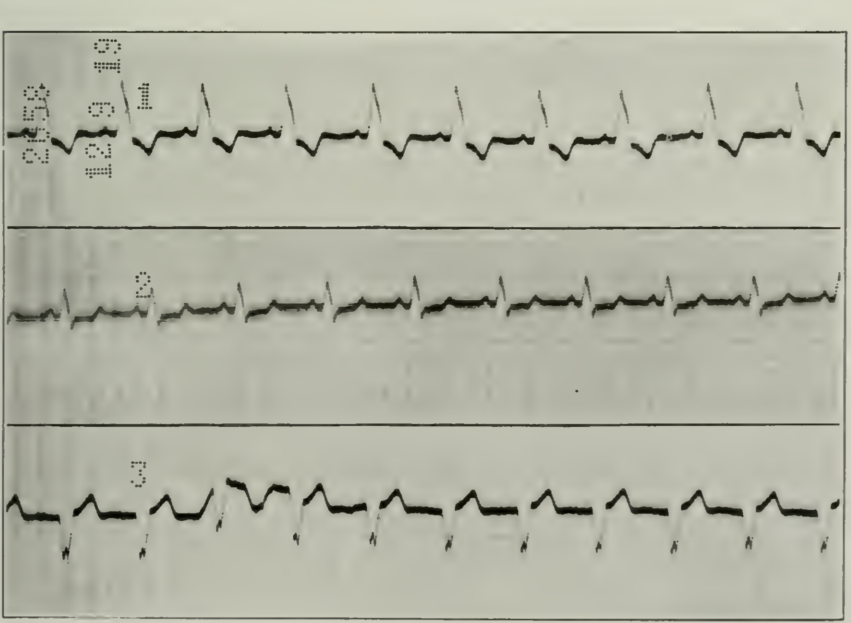
13 L. P. H. F.



14 L. P. H. M.



15 F. D. O. O.



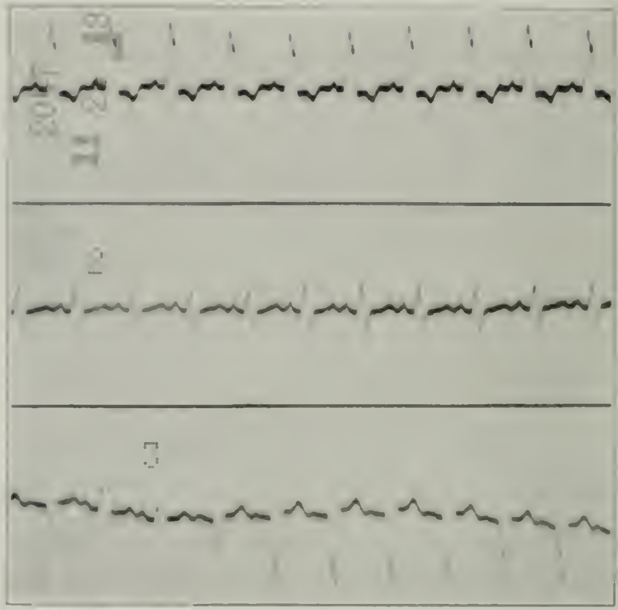
16 F. D. S. P.

Synapsis of Findings of Twenty Examples of Bundle Branch Lesions.

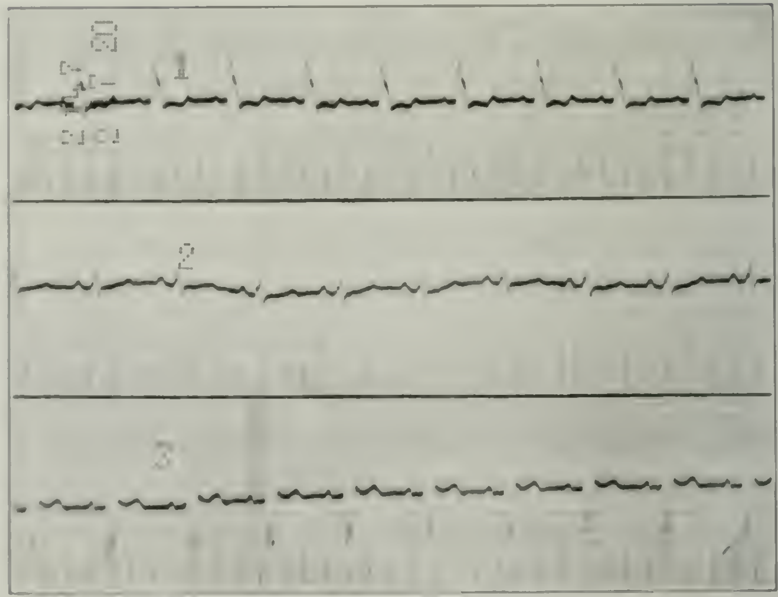
	Age	Sex	Probable Duration of Disease	Onset	Pain	Dyspnœa	Palpitation	Cough	Œdema	Rhythm	Blood Pressure	Valves	Murmurs	Response to Digitalis	Size of Heart	Diagnosis
L.P.P.P.	67	Male	1 yr.	—	Yes	Moderate	No	No	No	Normal 64	150/110	Moderate sclerosed	No	Good	Large aortic	Arteriosclerosis
L.P.B.B.	56	Male	1½ yr.	—	Oppression	On exertion	No	No	No	Normal 96	140/90	Aortic dis.	No	Fair	Normal; dilated aorta	
L.O.O.H.	52	Male	22 yrs.	—	No	On exertion	No	No	No	Normal with ex. syst. 88	—	Aortic and mitral dis.	No	—	Large	Valvular disease
L.H.H.I.	76	Male	Many yrs.	Dyspnœa	No	On exertion	When excited	No	No	Normal with ex. syst. 68	210/80	Aortic and mitral dis.	No	Fair	Moderate enlargement	Arteriosclerosis
L.P.H.F.	70	Male	5 yrs.	—	Stabbing	On exertion	No	Yes	Yes	Auricular Fibril. 75	190/100	Normal	Systolic	Poor	Much enlarged	Myocardial degeneration
L.P.H.M.	57	Male	8 mo.	—	Yes	On exertion	Yes	No	No	Normal 77	220/148	Normal	Systolic	—	Very large aorta	Cardiac dilatation
F.D.O.O.	80	Male	5 yrs.	Attacks of pain	Sharp	On exertion and with pain	No	No	Slight	Normal 68	low	Normal	No	Good	Large aorta	Angina pectoris
F.D.S.P.	58	Male	12 yrs.	Oppression	Oppression	None except at night	Yes in attacks	No	No	Normal 88	180/90	Normal	Systolic	Good	Very large aorta	Arteriosclerosis
F.D.I.O.	68	Female	8 yrs.	Attack nerv. exhaustion	Oppression	Moderate dyspnœa	Yes	Yes	No	Normal 70	180	Normal	Systolic	Good	Considerably enlarged aorta	Arteriosclerosis
F.L.I.O.	47	Female	8 mo.	Attack of pain	Sharp	Moderate	No	No	No	Normal 72	190/110	Mitral	No	—	Normal	Arteriosclerosis
L.H.L.M.	53	Male	3 yrs.	Gradual dyspnœa	Sharp	Marked	Yes	Yes	Marked	Heart Block 100	160/80	Aortic and mitral	No	Poor	Very large aortic	Valvular disease
L.S.O.D.	68	Male	5 mo.	Attack of pain	Severe, sharp	Moderate	Yes	Yes	No	Normal 84	150	Normal	No	Moderate	Mod. large aortic	Myocardial

Synapsis of Findings of Twenty Examples of Bundle Branch Lesions.—Continued.

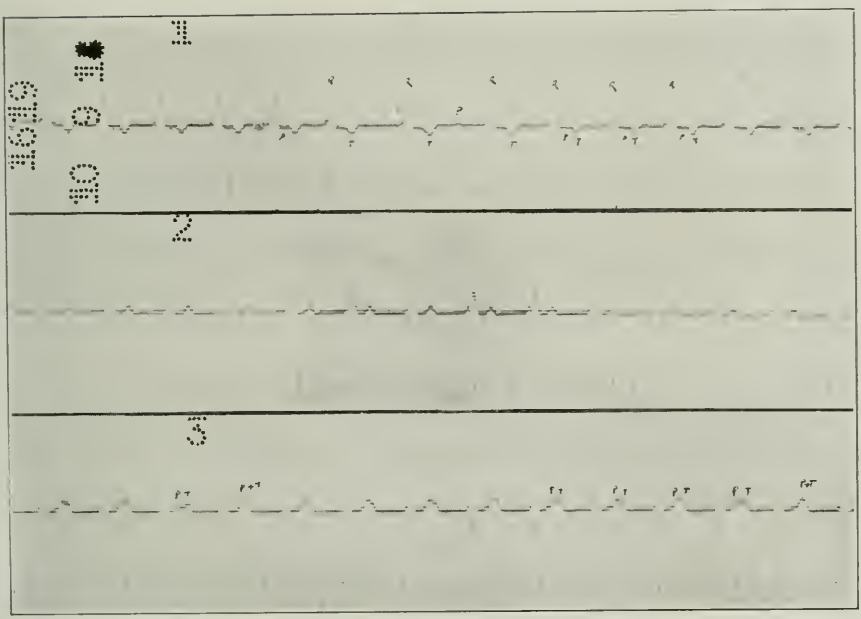
	Age	Sex	Probable Duration of Disease	Onset	Pain	Dyspnœa	Palpitation	Cough	Œdema	Rhythm	Blood Pressure	Valves	Murmurs	Response to Digitalis	Size of Heart	Diagnosis
L.H.B.D. .	55	Male	3 yrs.	Dyspnœa	Soreness	On exertion and attacks at night	Yes	No	At times	Normal 100	120/110	Normal	Systolic	Good	Very large	Myocardial
L.H.M.L. .	26	Male	Several years	Pain	Dull	No	No	No	No	Normal 72	—	Mitral	No	Poor	Normal	Valvular disease
L.O.D.I. .	52	Female	2 yrs.	Pain	Attacks severe, sharp	On exertion	Yes	Yes	No	Normal 96	160/80	Normal	Systolic	—	Normal broad aorta	Arteriosclerosis
F.D.M.P.	71	Male	1 yr.	—	Dull	On exertion	Yes	No	No	Normal 100	110/85	Aortic and mitral	No	Poor	Mod. large	Myocardial
L.S.P.L. .	68	Male	40 yrs.	Dyspnœa	Severe attacks and on exertion	Bad at times	At times	No	No	Normal 60	120/90	Mitral	No	Good	Large aortic	Rheumatism; cardiac disease
L.I.O.H. .	46	Male	—	—	Attacks severe	Bad at night and on exertion	No	Slight	No	Normal 75	145/110	Normal	No	Poor	Some hypertrophy	Arteriosclerosis, bronchial asthma
L.I.B.D. .	60	Female	5 yrs.	—	Dull	On exertion and smothering	On exertion	Yes	Moderate	Normal 120	140/105	Normal	Systolic	Fair	Mod. large	Myocardial
L.I.O.S. .	64	Male	9 mo.	Attacks palpitation	Occas. sharp	Good	Attacks	Yes	No	Normal with ex. syst. 88	200/80	Normal	Systolic	Good	—	Arteriosclerosis



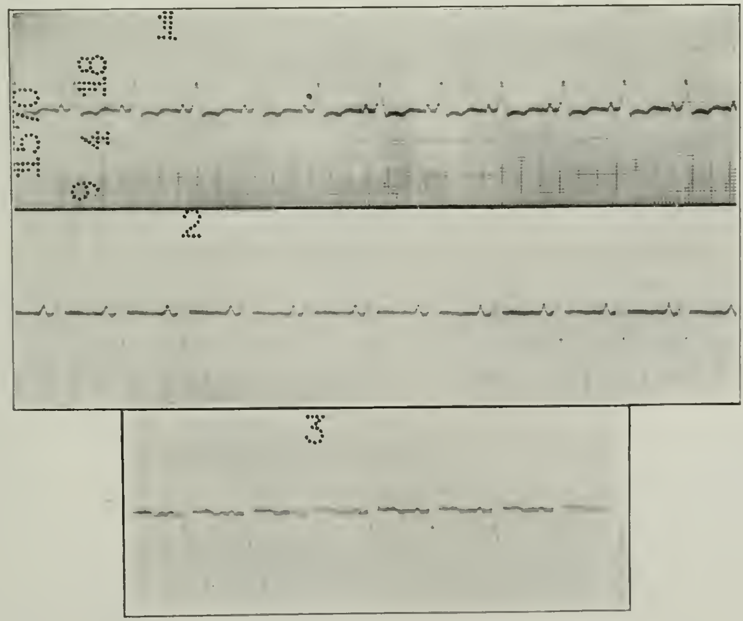
17 F. D. E. O.



18 F. L. L. O.



19 L. H. L. M.



20 L. S. O. D.

from a definite circulatory accident. It is analogous to the experience that slight attacks of hemiplegia are much better borne and more frequently recovered from among well-cared-for people than among a group ordinarily observed in hospital practice.

The most interesting conclusion to be drawn is that accidental interference with the circulatory system of the heart is probably very frequent and is not confined to those showing very striking clinical manifestations. It is possible that future studies may reveal some means of recognizing such an accident to other parts of the heart muscle. There is certainly much to learn from the study of such groups as these.

109 East 61st Street.

Discussion:

Dr. Oppenheimer: It is to be regretted that Dr. Bishop has not had any autopsy material in this series of cases, because at the present time the evidence on which our diagnoses of such electrocardiograms are made, rests largely on experimental work in dogs. The direct application of electrocardiograms resulting from experimental lesions in dogs to electro-cardiograms found in man is not certain for several reasons. There are anatomical peculiarities in the dog's heart as compared with the human heart, and the relation of the dog's heart to the chest wall differs from that in man. Moreover, experimentally a single isolated lesion in one of the chief branches of the bundle of His can be produced, but in human pathological material there are almost invariably diffuse, rather widespread lesions involving rather extensive areas of the heart muscle. Recently we have completed the detailed pathological study of two hearts obtained from patients who died in Roosevelt Hospital in the summer of 1914. Dr. Pardee had the opportunity of observing the cases, and of taking the electrocardiograms with the galvanometer in the physiological laboratory, and later we studied the serial sections at the pathological laboratory of the College of Physicians and Surgeons. We found lesions, but not absolutely complete ones, of the chief branches of the bundle of His, but the sides on which the lesions were discovered were the reverse of what we should expect from the results of the experiments on dogs originally performed by Eppinger and Rothberger, and subsequently confirmed by other investigators. In the first of our two cases, the main deflection was inverted in lead I, and upright in leads II and III; microscopic examination showed that the right bundle branch became so attenuated at a distance of 7.5 mm from the bifurcation that scarcely one or two doubtful muscle fibers could be seen; the left branch presented no lesion. The second case showed, on two examinations, electrocardiograms in which the main deflection was upright in lead I, and inverted in leads II and III. The left bundle branch was imbedded in dense fibrous tissue, and at a distance of 3.5 cm. below its origin, its posterior (dorsal) half was replaced by connective tissue continuous with an organized mural thrombus; the right branch was intact. These are only two observations, but they show the importance of the study of human pathological material in addition to animal experimentation in connection with electrocardiography.

Dr. Bishop: I want to thank Dr. Oppenheimer for his suggestion as to the side affected. I had been going chiefly on the empiric way we had been taught. I discussed a good many of these cases with Dr. Pardee, and he seemed to think they were as reported.

I would like to recommend to all of you the study of the electrocardiogram as a most interesting one. I am working with it every day, and every day it reveals something of interest.

A SIMPLER WAY OF PREPARING COLLOIDAL GOLD SOLUTION

MAX LEDERER, M.D.

(From the Laboratory of the Jewish Hospital of Brooklyn)

A perusal of the literature on the preparation of a satisfactory solution of colloidal gold for the detection of reducing substances in the cerebrospinal fluid and the evolution of a diagnostic curve, emphasizes the difficulties with which most workers meet. Most authors utilize some modifications of Lange's original method; either by varying the temperature of the solution during its preparation, or by adding one or more chemicals.

The author has tried most of these described methods and can testify to the inconstancy with which a suitable product has been obtained. For that reason, the following procedure is offered as practically uniform solutions conforming to accepted standards are obtained after almost every attempt.

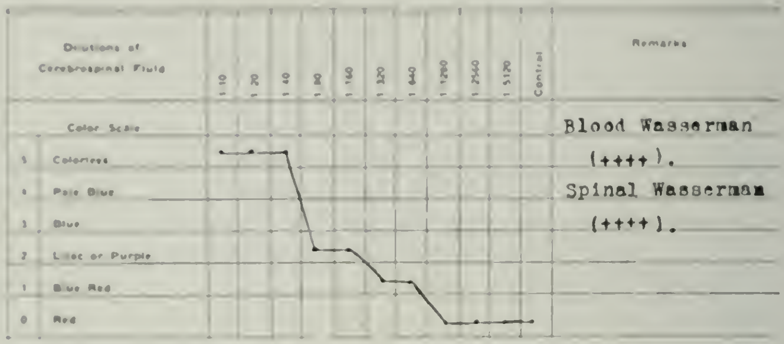
Solutions prepared in this manner have proven satisfactory in test before use; and clinically, the curves obtained have been checked up by other methods of bedside and laboratory diagnosis. The accompanying charts illustrate some of the results obtained in the wards and laboratory of the Jewish Hospital of Brooklyn.

The glassware used in the preparation of the solution is allowed to soak in freshly prepared aqua regia (U. S. Dispensatory formula) for three days.

Distilled water is made from an ordinary laboratory still. It is used without redistillation; but it is protected from contamination with dust. The glassware just before use is thoroughly rinsed with distilled water, and each article is tested with blue litmus paper, the rinsing being continued until no change in the blue color is noted.

REPORT ON COLLOIDAL GOLD REACTION

Diagnosis, General Paresis

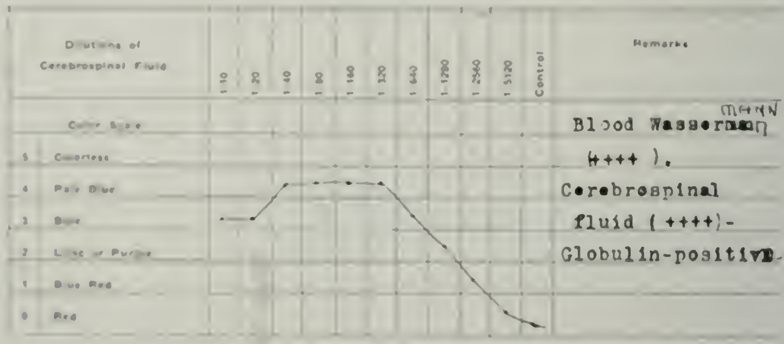


Blood Wasserman (++++).

Spinal Wasserman (++++).

REPORT ON COLLOIDAL GOLD REACTION

Diagnosis, Tabes



Blood ~~Wasserman~~ Wassermann (++++).

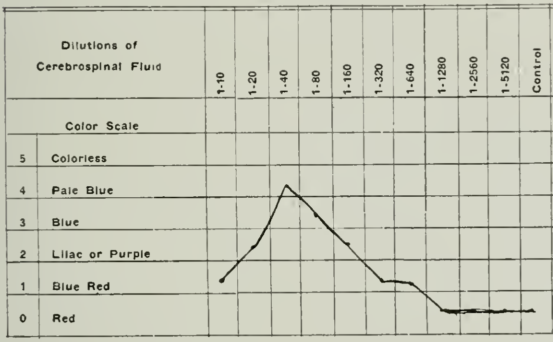
Cerebrospinal fluid (++++)-

Globulin-positive.

Into a liter Erlenmeyer flask is poured 500 c.c. of distilled water, accurately measured. Add 5 c.c. of a 1 per cent. solution of gold chloride (Merck and Co.), 3.5 c.c. of 2 per cent. potassium carbonate solution, 0.87 c.c. of 1 per cent. oxalic acid solution and 0.2 c.c. of a 2.5 per cent. solution of formalin. Place over a flame, protecting the base of the flask with a square of asbestos, and heat gently until swirls of water begin to rise to the surface. Adjust the flame so that the temperature of the solution remains at this point, for about 40 to 45 minutes, but do not permit bubbling to occur. At the end of this time the solution should become dark.

Report on Colloidal Gold Reaction

Diagnosis, C. S. Lues

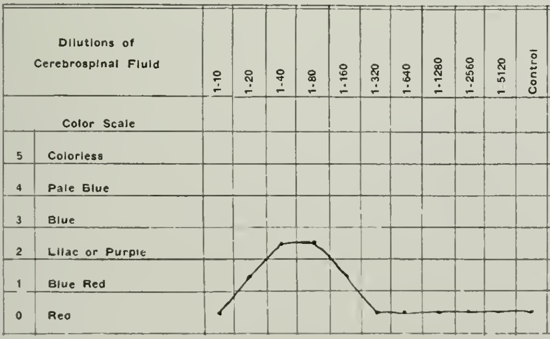


Remarks

Blood Wasserman
positive(++++))
Cerebrospinal
fluid--
Globulin-positive
Wasserman (++++).
50 lymphocytes.

Report on Colloidal Gold Reaction

Diagnosis, C. S. Lues



Remarks

Globulin ++++
C. S. Wasseman
positive ++++
Blood Wasserman
4+.
Responded to
Arsphenamine

When this is noted add slowly drop by drop more formalin solution, meanwhile gently agitating the fluid by a rotatory movement of the flask. Soon there will be seen a brownish red discoloration following in the wake of the formalin drop. The solution becomes darker and darker, changing to a reddish color, and suddenly it takes on the typical old rose hue. The flask is then removed from the flame and allowed to cool.

The amount of formalin used varies in amounts of from about 1.7 to 2.2 c.c. In preparing several batches of solution at the same time, each one may require a different amount. Why this happens we do not know, and no investigation as to the cause of this inconstancy has been attempted by us.

However, in our laboratory, we have met with almost uniform success in every attempt to prepare this fickle solution. It has been used for over a year, and clinically, it has proven satisfactory.

Discussion:

Dr. Rohdenburg: We have been using practically the same technique as that described by Dr. Lederer, and I simply want to reinforce his statement that the bugbear of getting a good solution disappears with that technique. The trouble with colloidal gold solutions seems to be with the formaldehyde. The various niceties of method that have been used, such as the triple distillation of water, etc., have apparently very little influence. We had our first consistent success in making the solution when we received a batch of formaldehyde in one pound bottles instead of in the usual fifty pound carboy. In small containers the formaldehyde does not deteriorate, nor increase its acidity greatly, whereas in a big carboy which is frequently opened and left there is a very marked reduction in the formaldehyde content and an increase in acidity. I think the major part of the technique trouble is due to the variations in the formaldehyde.

Dr. Stillman: I would like to second Dr. Rohdenburg's remarks about the formaldehyde. We soon discovered that it was the variations in different batches of formaldehyde that caused the trouble. We have been using Lee's method which is also very simple and gives little trouble since we appreciated the variation of the strength of the formaldehyde.

Dr. Lederer: I fully agree that the formalin is the chief factor that we have to deal with. How much of the formalin evaporates on the addition of the formaldehyde as some writers advise I do not know. I think another cause that results in failure is usually the chemical uncleanliness of the glassware. I find that some workers are just a little bit careless. They think as long as they do not see any dirt on the glass that they will get good results. I find also that if one avoids the use of soaps that one is likely to get better results. We do not use soaps in the preparation of the glassware. We also use instead of large test tubes small test tubes—the regular Wassermann tubes, 4 x ½ inches, and we can read the end results far better than with the larger tube.

PRECIPITIN FORMATION IN A PATIENT WITH SERUM DISEASE SHOWING IMMEDIATE AND ACCELERATED REACTIONS

GEORGE M. MACKENZIE, M.D.

(*From the Medical Clinic of the Presbyterian Hospital, New York City*)

Since the pioneer work of von Pirquet and Schick (1) on serum disease, it has been recognized that patients previously treated with heterologous serum may, upon reinjection, exhibit any one of three types of reaction. The type of reaction, or rather, the time when the reaction occurs, depends, they thought, upon the interval between the first and second injections. (1) If the second administration of serum is made twelve to forty days after the first, an immediate reaction occurs. This reaction may be local or general or both, and may be characterized by local œdema at the site of injection, skin eruptions, fever and œdema. The immediate reactions last only one to two days. (2) If the interval between the first and second injections is six weeks to six months, an immediate reaction is apt to occur and also what they called an "accelerated" reaction. In the latter, the symptoms are the same as those of the immediate reaction, but the incubation period is five to seven days; the usual incubation period after a first injection is approximately eight to twelve days. The accelerated reaction like the immediate reaction may last only a day or two. (3) If the second injection is more than six months after the first, only the accelerated reaction is to be expected. The time intervals necessary for these types of serum reaction are subject to considerable variations, von Pirquet and Schick believed.

This patient with serum disease showing both immediate and accelerated reactions was a young man of American birth, 22 years old, admitted to the Presbyterian Hospital, March 21, 1920. Since the condition which brought him to the hospital was of no especial interest from the point of view of his serum disease, only a brief outline will be given.

Chief Complaint: Fever, cough, and pain in left chest for four days.

Family History. Nothing to suggest phenomena of hypersensitiveness in any other members of the family.

Past History. Patient had measles in childhood; pneumonia at the age of eight, and influenza in 1918. Seven years ago he had diphtheria and was given antitoxin. Two years ago, while in the Navy, he had cerebrospinal meningitis and was given anti-meningococcus serum intraspinally. The amount of serum given is not known, but about two weeks later he had a severe attack of urticaria and his eyes swelled so that he could scarcely see. These symptoms persisted several days. He had no recollection of any previous attack of urticaria and had never had angioneurotic edema, eczema, hay fever or asthma.

Present Illness. Four days before admission he had a chill followed by a temperature of 104° F. He had cough, blood-streaked sputum and pain in the left side of the chest.

Physical Examination upon Admission. Temperature, 105.8°. Pulse, 118. Respiration, 20. Patient appeared acutely ill and had signs of a small area of consolidation in the left lower lobe.

Blood Count. White blood cells, 22,400. Polymorphonuclears, 92 per cent. Lymphocytes, 8 per cent. Hemoglobin, 90 per cent. (Sahli). Blood culture was sterile, the Wassermann negative.

Urine. Specific gravity 1.012 to 1.022; acid; albumen, 0; glucose, 0; microscopic showed nothing pathological.

The details of his pneumonia will not be given. It ran an uneventful course; the temperature came down by lysis and the signs in the left lower lobe cleared up promptly.

The interesting feature was the result of giving horse serum to this patient who had twice previously been injected with horse serum—seven years ago for diphtheria and two years ago intraspinally for meningitis. On the latter occasion he reacted with the usual form of serum disease following a first injection.

Upon admission, it was found that he gave a strongly positive reaction to the intracutaneous injection of 0.02 c.c. of a 1:10 dilution of horse serum. Since the usual method employed for desensitizing such patients requires several hours, the house staff started to desensitize him before receiving a report of the mouse inoculation for pneumococcus grouping. It turned out to be a Group IV pneumonia, but this was not known until efforts at desensitization had been carried as far as possible with the idea of preparing him for a large dose of antipneumococcus type I serum.

The following table shows how the desensitizing doses of serum were given:

Time	Horse Serum, Cc.	Method of Administration	Reaction
10.30 P.M. . .	0.025	Subcutaneously	None
11.00 “ . .	0.05	“	“
11.30 “ . .	0.1	“	“
12.00 M . .	0.2	“	“
12.30 A.M. . .	0.4	“	Slight difficulty in breathing
1.00 “ . .	0.8	“	Erythema, site of injection
1.30 “ . .	1.0	“	None
2.00 “ . .	0.1	Intravenously	“
2.30 “ . .	0.2	“	“
3.00 “ . .	0.4	“	“
3.30 “ . .	1.0	“	Swelling, lower jaw.
4.00 “ . .	2.0	“	None
4.30 “ . .	4.0	“	“
5.00 “ . .	8.0	“	“
5.45 “ . .	16.0	“	Erythema on dorsum of fingers, around left eye and on forehead.

A few minutes after the intravenous injection of 16 c.c. of horse serum at 5.45 A.M., the erythema became generalized and the patient complained of itching of the hands, back and face. Urticarial wheals appeared over the elbows, wrists and knees. There was no respiratory embarrassment, no œdema nor arthralgia. Five hours later, there was still a diffuse eyrthema. This gradually disappeared during the next twenty-four hours. Two days later, that is, three days after the administration of horse serum, the epitrochlear and axillary lymph nodes enlarged and there was a generalized eruption which at first was morbiliform and then urticarial. A few purpuric spots were also noted. Soft œdema appeared on forehead, eyelids, nose, lips, forearms, feet and penis. This second serum reaction persisted for six days. The patient therefore showed an immediate and an accelerated reaction, the latter having an incubation period of three days.

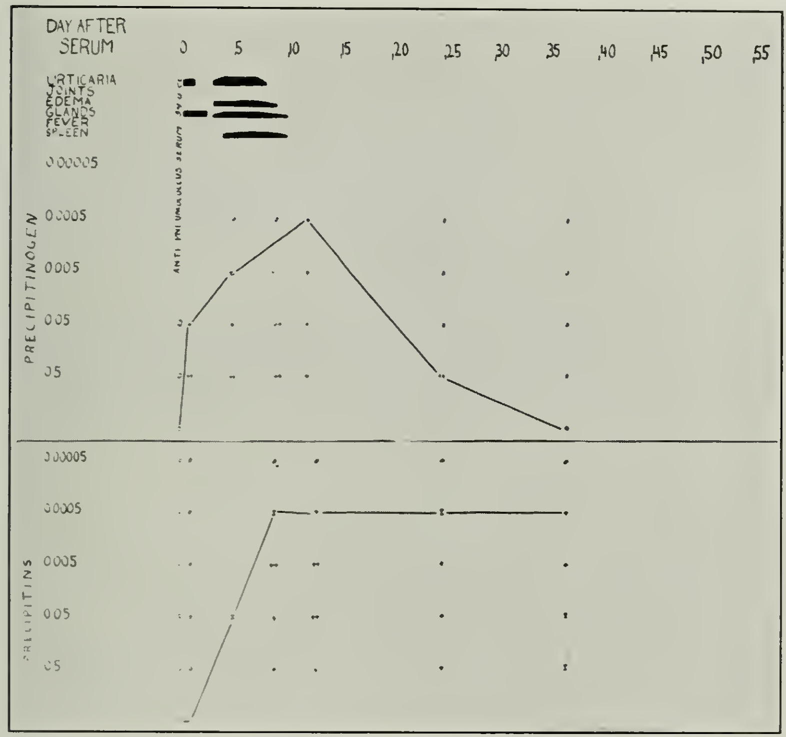
We have been studying the curves of precipitin and circulating antigen in cases of serum disease and it was therefore with a good deal of interest that we followed these curves in this individual who twice previously had been treated with horse serum and who at the time when the 34.0 c.c. of anti-pneumococcus serum were given was demonstrably hypersensitive. Text-figure 1 represents graphically the development of precipitins and the length of time during which horse serum persisted in the circulation. The relation of these curves to the serum disease is also shown.

There are two points illustrated by this patient to which we wish to call attention.

First, the inadequacy of the Besredka and similar methods of desensitization in man. Besredka's (2) procedure is as follows: One c.c. of a one to seven dilution of the serum is injected intravenously. After 3 to 5 minutes, 3 c.c.; after 2 minutes, 10 c.c; after 2 minutes, 25 c.c.; after 10 minutes, the patient is considered antianaphylactic and 10 to 30 c.c. of undiluted serum may be given intraspinally or intravenously. As shown in Chart I we began the desensitization program with a much smaller dose and gave it subcutaneously. We increased the amounts more slowly and gave them at longer intervals than Besredka advises. Nevertheless, when the intravenous dose of 16 c.c. was given, he reacted with such severe symptoms that it would have been dangerous to go ahead with larger doses. It is often stated that a preparatory injection of 1.0 c.c. of serum, subcutaneously, will desensitize a patient so that, after an interval, large doses may be given with impunity. Our experience with this patient shows how inadequate such methods may be with hypersensitive patients.

The second point we wish to emphasize is the accelerated antibody formation parallel with the accelerated symptomatic reaction. After first injections, precipitins usually appear several days after the onset of serum disease, and rise to the crest of their curve synchronous with the termination of the symptoms and the disappearance of the precipitinogen from the circulation. Since the usual incubation period is eight to twelve days, precipitins are rarely found in the circulation earlier than the tenth day. In the paper of Hamburger and Moro (3) precipitins are reported as making their first appearance between the sixteenth and the twenty-seventh day; von Pirquet and Schick (4) state that in children treated with diphtheria antitoxin, precipitins appear toward the end of the third week. In the fifteen cases reported by Longcope and Rackaman (5), precipitins did not appear earlier than the ninth day. Another group of fifteen patients with serum disease after first injection, in whom we have studied precipitin and precipitinogen curves, has revealed only one example of demonstrable precipitins before the ninth day.

It has been repeatedly demonstrated that if rabbits are reinjected after the precipitins produced by a first injection have disappeared from the circulation, that precipitins are formed more rapidly than after the first injection. This patient is an example of the same phenomenon in man. As shown in Text-figure 1, precipitins were present on the fifth day, and they rose to the crest of the curve at the time that the symptoms of the serum



TEXT-FIGURE 1. Abscissa represents time in days after administration of serum. The ordinates represent the dilutions of antigen used in testing for precipitin and precipitinogen (horse serum). The results of the precipitinogen titrations are plotted in the upper curve, those for precipitin in the lower. It is seen that precipitin was present on the fifth day, and still present in high concentration thirty-seven days after the administration of serum. With the rise of the precipitin to a high concentration (1–2,000) the precipitinogen curve falls and the symptoms cease.

disease were subsiding. The whole process seems to be accelerated after a second injection, so that the incubation period for both symptoms and precipitins is shortened. The precipitins, however, stand in the same relation to the onset and termination of the symptoms. This interesting relation between the precipitins in the circulation and the symptoms of the serum reaction, cannot, of course, be interpreted as indicating that precipitins are responsible for the serum disease. The weight of evidence is in favor of the view that serum disease is an antigen-antibody reaction and that it is only the intracellular antibody which is responsible for the phenomena of the reaction. Precipitins, however, appear in the circulation, sometimes in high concentration, sometimes in low. Just what part the circulating precipitin plays in the reaction, it is not possible to say, but it is nevertheless worth recording that in a hypersensitive individual showing immediate and accelerated reactions, there was also an accelerated appearance of precipitin in the circulation.

References

1. von Pirquet and Schick: Die Serum Krankheit, 1905. Leipsic and Vienna.
2. Besredka, A.: Anaphylaxis and Antianaphylaxis (Trans. Gloyne), St. Louis, 1919.
3. Hamburger, F., and Moro, E.: Ueber die biologische nachweisbaren Veranderungen des Menschlichen Blutes nach der Seruminjection. *Wein. klin. Wchnschr.*, 1903, xvi, 445.
4. *Ibid.*
5. Longcope, W. T., and Rackemann, F. M.: The Relation of Circulating Antibodies to Serum Disease. *Jour. Exper. Med.*, 1918, xxvii, 341.

Discussion

Dr. Jobling: I should like to ask if there is any relation between the reaction and the concentration of the precipitinogen in the serum.

Dr. Mackenzie: Apparently there is no definite relation between the titer of the precipitinogen in the circulation and the severity of the reaction.

Proceedings

of the

New York Pathological Society

New Series, Vol. XX OCTOBER-DECEMBER, 1920 Nos. 6-8

CONTENTS

PAGE

A Tumor of the Thymus Gland. *G. L. Rohdenburg, M.D.* 97

Experimental Syphilis. *Wade H. Brown, M.D.* 99

The Relation Between Spermatogenesis and Leucopoiesis in Acute Infection. *Henry E. Meleney, M.D., and Harold Linsky, B.S.* 117

Vitamines and the Avitaminoses. *Casimir Funk, D.Sc.* 119

Besredka's Method of Oral Immunization of Rabbits With Ox-Bile and Paratyphoid Vaccine. *Abraham Zingher, M.D., and David Soletsky, M.D.* 133

Quiescent Metastatic Gastric Carcinoma. *G. L. Rohdenburg, M.D.* 141

Metastasis of Carcinoma into an Endothelioma of the Optic Sheath. *Martin Cohen, M.D., and Ward J. MacNeal, M.D.* 145

The Experimental Production of Sarcoma of the Liver of Rats. *F. D. Bullock, M.D., and M. R. Curtis, Ph.D.* 149

Dr. James W. Jobling, *President.*

A TUMOR OF THE THYMUS GLAND

G. L. ROHDENBURG, M.D.

(*From the Laboratory of the Lenox Hill Hospital, New York City*)

The rather frequent reports in the recent literature are evidence that tumors of the thymus gland are not as rare as was once supposed. It is with the idea of adding to the existing data that the following case is presented.

The clinical course of the disease in this patient is rather atypical. The tumor occurred in a male, Hebrew, forty-five years old, a furrier by occupation, who had been under observation at varying periods for over three years. He complained on his first admission to the hospital of a persistent cough and after a period of observation lasting five days he was discharged without a decision as to the origin of the cough. He was again admitted to the hospital a year later, again complaining of cough, profuse expectoration, a loss of weight and shortness of breath. Repeated examinations of the sputum were negative for tuberculosis, although the physical signs in the chest pointed to a widespread and active process involving both lungs. His temperature varied from 98.6° to 102.4° F. He was somewhat emaciated and had lost twenty-five pounds in the year. A radiographic examination of the chest showed a sharply demarcated shadow in the region of the left auricle, and percussion of the cardiac outlines showed an area of dulness agreeing with the radiographic findings. His lungs when examined radiographically showed a picture described as a diffuse tuberculosis. The diagnosis on his discharge was pulmonary tuberculosis, and congenital heart lesion.

He was admitted to the hospital for the last time, two years after his second discharge, and two days before his death. Upon admission, his chief complaint was a furuncle of the lower lip about which there was a diffuse and extensive induration. During his short stay his temperature rapidly rose to a terminal one of 108° F.; he became first maniacal and then comatose, and died of pulmonary edema. He had become so emaciated that his thigh could be spanned with one hand, and it was estimated that he had lost an additional fifty pounds. His relatives stated that the cough had persisted, and that it had become increasingly more difficult for him to breathe. The physical signs in the chest were the same as those on his second admission, except that they were more extensive. Radiographic examination of his chest showed an increase in size of the mass over the left auricle, though it was still sharply demarcated and definite in outline. His pulmonary condition showed little or no change as compared with the process two years previous. His urine contained six per cent. sugar, with acetone and diacetic acid.

At the autopsy the chief point of interest was in the chest, the abdominal viscera showing the parenchymatous degeneration so often seen with septic conditions. Upon opening the chest there presented in the position of the thymus what at first glance appeared to be an enormously hypertrophied gland, the usual configuration being accurately preserved. The gland measured 12 x 14 x 8 cm. in its greatest diameters and overlapped the heart, being tightly adherent to the pericardium. Section through the thymus showed it to be a golden yellow color and to be very firm and resistant on section. There were a few areas of softening in the central portions of the growth. Upon opening the pericardium about 45 c.c. of a clear fluid escaped. On the ventral surface of the heart along the median line were a series of nodules varying in size, the largest being 1.25 cm. in diameter, extending from the main tumor mass. The parietal side of the pericardium showed similar smaller masses. The lungs showed a series of symmetrically distributed hemorrhagic firm areas which on section appeared to be infarcts, and most of which were situated directly beneath the pleura. The larger of these areas measured 2 cm. in diameter. There were no other demonstrable metastases.

Microscopical examination of the tumor showed it to consist of larger and smaller acini of clear cuboidal cells densely packed together and supported by dense noncellular hyaline connective tissue. Intracellular connective tissue fibrils were not demonstrable. These neoplastic cells were also found similarly arranged in the lesions of the pericardium. In the lung the masses previously described consisted of areas of necrosis surrounded by an inflammatory reaction. In the center of these necrotic areas tumor elements could occasionally be demonstrated.

There is, as is well known, considerable confusion regarding the classification of tumors in the thymus. Ewing draws attention to the fact that while most of the French reports concern carcinoma, most of the German communications describe the neoplasms as sarcoma. Because of this confusion, the term thymoma has been proposed. The tumor in the present instance, however, is to be classed most probably as a carcinoma.

EXPERIMENTAL SYPHILIS

WADE H. BROWN, M.D.

(From the Laboratories of the Rockefeller Institute for Medical Research, New York)

The interest which an experimental infection holds for the pathologist is as an instrument for the investigation of problems of human disease, and in the case of syphilis there are innumerable problems which have been difficult or impossible of approach on account of the lack of a suitable animal infection. If one wishes to employ an experimental infection for the study of problems of human disease, it is not sufficient that the infection be transmitted to laboratory animals, but it is equally essential that it be brought to a state where the analogy between human and experimental conditions is as close as possible and that one possess an intimate knowledge of both the animal and the human infection. The sequence of events in the development of an experimental infection for such a purpose as I have indicated is, therefore, first, transmission, second, modification and adaptation, third, detailed study of the infection produced, and finally application to problems of human infection.

The transmission of syphilis to laboratory animals is not new; infections differing somewhat in type have been produced in apes, monkeys and rabbits. The infection of apes and of monkeys, although more analogous to the human disease than that originally produced in the rabbit, cannot be very widely used in the study of human syphilis. For such work, the experimental animal should be inexpensive and the rabbit appears to offer the best opportunity for carrying out such studies upon a broad scale.

The difficulty which has arisen in the use of the rabbit has been the nature of the infection produced. Rabbits have been successfully inoculated in the eye, the testicle and various skin areas of the body but it was found that very little developed in these animals except a local lesion at the site of inoculation. It was shown in some instances that the organisms migrated from the point of inoculation and they were recovered from the lymphnodes, spleen, bone marrow, blood and other organs. In isolated instances, lesions were noted at points entirely removed from the site of inoculation. The first case of this kind was reported by Grouven in a series of communications which appeared during 1907 and 1908. This animal was inoculated in both eyes but infection developed in only one; the eye was enucleated and following this, lesions appeared in the skin and mucous membrane and in the opposite eye; there were marked constitutional symptoms and at autopsy spirochetes were demonstrated in the testicles and regional lymphnodes. As a matter of fact, nearly all of the lesions which have since been described existed in this first case of generalized syphilis in the rabbit.

Other instances of generalized lesions have since been reported but the lesions present were few in number and of a minor character. The most common conditions noted were involvement of the eyes with the production of an interstitial keratitis, papular lesions of the skin and metastatic lesions of the testicles.

When it was found that the disease produced in the rabbit by ordinary methods of inoculation tended to remain a local one and did not lead to the production of generalized lesions as in man, the attempt was made to produce such a condition by intravenous or intracardial injections of massive doses of spirochetes. After a number of failures, these attempts were in a measure successful in that it was shown to be possible to produce a variety of lesions in animals thus inoculated and that such conditions could be produced with much greater frequency than by local inoculation. It should be pointed out, however, that since the dissemination of organisms in these animals existed *ab initio* in virtue of the mode of inoculation employed, there are some valid objections to considering this type of infection as a generalized syphilis comparable to that which occurs in the acquired form of the disease in man.

This was the status of the subject when we began the study of experimental syphilis. Our interest in this subject originated through an effort to use the experimental infection as a means of studying the action of therapeutic agents but it was soon found that existing knowledge of the infection in the rabbit afforded no adequate basis either for the conduct of the experiments or for the interpretation of results. These limitations naturally obtained also in the study of other problems of human syphilis.

In an effort to meet these conditions, we attempted to gain a more intimate knowledge of the manifestation of infection in the rabbit and to produce an infection which was better adapted to the needs of the investigator. For a period of years, our work consisted largely of observation and record upon material which was being used in the course of other work with little or no opportunity to attempt anything more. In this way, we were able to collect and to study a number of animals which had developed generalized lesions of various types following inoculation in the scrotum or testicles.

The problem which had to be solved if one would reach an intelligent understanding of the experimental infection was why an animal should develop lesions at the site of inoculation but none elsewhere, even though the organisms penetrated the lymphatics or gained access to the blood stream and were widely distributed over the body. At first sight this would seem rather difficult to explain and we did not know whether this dissemination of organisms was constant or only occasional. The point at which our experimental work began, therefore, was the determination of the time and frequency of generalization of the infecting organisms following inoculation in the testicles or scrotum.

A large number of experiments was carried out for the purpose of determining the presence of spirochetes in the regional lymphatics and the circulating blood. To do this, animals were inoculated in the scrotum by the introduction of a bit of infected tissue; at various intervals after inoculation, the inguinal nodes were removed, ground in a mortar and an emulsion prepared and injected into the testicles of normal animals; the presence of spirochetes in these nodes was decided by the development of an infection in the test animal. In another series of experiments, blood was drawn from the hearts of rabbits which had been inoculated in the testicle or scrotum; after defibrinating, 0.5 c.c. of blood was injected into the testicles of test animals.

In this way, it was found that spirochetes could always be recovered from the inguinal lymphnodes within forty-eight hours after a scrotal inoculation and from the circulating blood within one week after a testicular inoculation, thus showing that a widespread dissemination of the infecting organisms always occurred at a period well in advance of the appearance of the primary lesion.

This being true, the question naturally arises as to why such animals develop no generalized lesions except in an occasional instance? To one familiar with the rabbit infection, the first point which is apt to attract attention is the marked character of the reaction at the site of inoculation. Among the animals studied by us, it was frequently noted that in instances where generalized lesions developed, the primary lesions were very small or slight and this observation gave us our first clue to the cause of the anomalous character of the animal infection.

Upon examination of the records of those animals which had developed generalized lesions, it was found that in the great majority of cases, one of several conditions had existed: Either the lesion at the site of inoculation had been slight or the animal had been subjected to castration or excision of the primary lesion, or some therapeutic agent had been used which had the effect of reducing the lesion present without destroying the infecting organisms. An investigation of the cases of generalized syphilis reported in the literature revealed the fact that most of these had also occurred under a comparable set of conditions. In this instance, either the animal had been inoculated at one instead of several points or the initial lesion had been excised.

It appeared, therefore, that the presence or absence of generalized lesions was bound up with the primary reaction to infection. We then undertook to determine experimentally whether conditions which tended to reduce or suppress this reaction might not have an influence upon the development of lesions elsewhere. The conditions studied were unilateral as contrasted with bilateral inoculation, the effects of castration or excision of primary lesions, the suppression of primary lesions by the use of therapeutic agents, and the complete prevention of a primary reaction.

The animals were held under observation for three to four months, the results of the experiments being determined by the occurrence of such lesions as could be recognized clinically within this period of time.

The results of the experiments shown on the chart may be summarized as follows:

In group I there were 20 animals which were inoculated in both testicles; 6 were held as controls and 14 were castrated at an early stage of the infection. In this case, 1 of 6 controls developed generalized lesions as compared with 13 of the 14 castrated animals.

In group II there were 27 rabbits inoculated in only one testicle; 13 of these were used as controls and 14 were castrated as in group I. This time, 8 of the 13 controls and 13 of the 14 castrated animals showed generalized lesions.

In a third group of animals, resolution of the lesions was induced by the use of a therapeutic agent administered in doses which were incapable of destroying the spirochetes. There were

24 animals in this group: 12 of them were inoculated in both testicles and 12 in only one testicle. Out of 6 controls in the first series, 1 developed generalized lesions as compared with 5 of the 6 treated animals; in the second series 3 of the 6 controls and all (6) of the treated animals showed well-marked generalized lesions.

In a fourth group of experiments, an attempt was made to determine what effect would be produced if instead of permitting the primary lesions to develop as in the preceding cases, one completely suppressed the reaction at the site of inoculation by amputating the testicle and scrotum forty-eight hours after inoculation. There were ten rabbits in this series which were inoculated in the right scrotum by means of an implant. At the end of the first seven weeks after inoculation, eight of them had developed generalized syphilis which is unusually early and the other two developed generalized lesions before the experiment was concluded, thus giving an unbroken and a very marked series of cases of generalized syphilis.

These experiments appeared to supply a basis for an understanding of the reaction to infection in the experimental animal and at the same time provided means of producing a generalized disease in the rabbit which is more analogous to that which occurs in man. Further than this, I shall not attempt to go.

The next point to be considered is what one means by generalized syphilis in the rabbit. In the generalized disease a variety of lesions occurs chiefly in the skin, the mucous membranes, the eyes, the periosteum and the bones. We have thus far seen practically no visceral lesions with the exception of a few granulomatous conditions which occur in the heart. We know very little of syphilis of the central nervous system. As you know, lesions of the central nervous system have been described, but one must be very cautious indeed in speaking of lesions which occur in the nervous system of the rabbit, since lesions analogous to those which might be produced by a syphilitic infection are found in supposedly normal animals. We have shown, however, that spirochetes do invade the cerebrospinal axis of the rabbit.

We have been able to demonstrate them by inoculation of cerebrospinal fluid, free from blood, in three animals out of thirteen attempts. One of these was a comparatively early infection and the two others showed active generalized lesions.

The character of the lesions which occur in the rabbit is best shown by illustration. For this purpose we have collected a series of photographs showing the lesions present in representative cases of infection and while they do not include all of the lesions which occurred, they will nevertheless afford a fair impression of the various types of lesions and will show something of the condition which existed in the individual animal. On the whole, they represent the more marked cases of generalized infection.

Generalized syphilis in the rabbit is a very variable condition, as it is in the human subject, and hardly any two animals show precisely the same thing. The lesions usually appear in from two to three months after inoculation and the order in which they appear in different tissues is in general: periosteum and bone, skin and mucous membranes, and finally the eye. The lesions of the several systems vary in different animals. Those of the skin tend to conform to one of two general types. Most frequently they are nodular or tubercular syphilides or they might be called gummata. Again, they resemble more closely the earlier lesions that one finds in cases of human syphilis—there are small infiltrations or macules and papules or maculo-papular lesions showing various degrees of desquamation, exfoliation, necrosis, ulceration and so forth. It is an interesting fact also that the type of lesion present in the individual animal tends to conform to the type of the primary lesion in the scrotum.

The first example which I wish to show is that of an animal with a profusion of small infiltrative lesions of the skin which were distributed about the head and ears, over the forearms, the dorsum and sides of the front and hind feet, and the tail. There were lesions also along the naso-labial margins and in the nasal mucosa. The manifestations of active infection in this animal extended over a period of approximately eight months and the case was one of almost pure cutaneous syphilis.

As a contrast to this, I wish to show a second case of cutaneous syphilis in which all of the lesions were of the large granulomatous type. This animal was inoculated in the right testicle and developed large skin lesions in the scrotum and large granulomatous lesions of the forearm, on the lower eyelid, and on the hind feet and legs. There was also a marked lymphadenitis and a few bone lesions, one of which may be seen at the base of the metatarsal. All of these lesions developed within a period of approximately two months.

A third animal, in which the skin lesions were of the same type as those just shown, furnishes an illustration of a much more pronounced and widespread infection. There was a profusion of skin lesions involving the face, the base of the ears, the front feet and legs, the hind feet and legs and the tail; there were lesions of the bones of the forearm, of the external malleoli and of the long bones of the feet; there were also mucous lesions on the shaft of the penis and about the nares and finally there were lesions of the cornea and iris.

Lesions of the bones in experimental syphilis are among the most interesting manifestations of the generalized infection and this card will show what the common ones are. The most frequent are those which occur about the nose; these are usually periosteal in origin, developing from the outer surface of the bone. They may arise from its inner surface, however, or within the substance of the bone. Lesions in this position frequently result in marked bone destruction and produce a typical saddle nose deformity such as that shown in the radiograph. A second common location of bone lesions is the forearm; the one shown was located near the epiphyseal line of the ulna. The effect upon the bone in this instance is indicated in the corresponding radiograph. The location of lesions near the epiphyses is very common. A third type of lesion is that seen at the base of the fifth metatarsal and these frequently lead to marked destruction of the bone. These illustrations are not all from the same animal but are pronounced or characteristic examples intended to give an idea of the nature of the lesions in the several localities.

The next series of photographs is taken from a case that we might call bone syphilis since with one or two exceptions the lesions present were all of this type. The photograph of the head shows a slight deformity over the nose which does not appear striking at first glance, but the skull of the animal shows marked destruction of the nasal bones. Distinct lesions are seen at the carpus of both forearms. Very pronounced lesions occur also over the external malleoli and others extend along the outer side of the hind feet involving the metatarsals and the phalanges. The animal affording all these lesions also showed a marked lymphadenitis.

At this point, I should like to call attention to the fact that many of the lesions which occur in the rabbit are more analogous to those of congenital than of acquired syphilis and this applies particularly to the lesions of bones.

The conditions shown thus far represented manifestations which arose within a comparatively short period of time. We have, however, similar records of animals which have been held under observation for much longer periods of time—one indeed which is still alive, has been under observation for four years and four months and now shows a lesion of the scrotum which has appeared quite recently. A second rabbit was carried for thirty-three months before it was killed. This group of photographs which was taken from this animal shows some of the most pronounced lesions that we have ever observed. As you see from the photograph of the head taken at autopsy, there was a periosteal lesion of the nose and a lesion in the skin and these had been present for considerably more than a year. Originally there were a number of skin lesions on the feet and legs, some of which are indicated by the very large nodules on the outside of the feet. One lesion on the heel was excised in order to get material for transfer but recurred several times. The photograph is of one of the recurrences. A second lesion with a very interesting history is that at the base of the fifth toe. It was one of the original lesions and persisted from the time of its first appearance until the death of the animal, that is, for more than two years. Another very persistent lesion of this group is shown on the forearm and this was of approximately thirty months' duration.

This animal also had the most marked eye lesions which we have observed. A keratitis appeared about three months after inoculation: there were repeated exacerbations of this condition and a lesion of the cornea was present when the animal was killed. There were also repeated attacks of iritis, and the photograph of the eye was taken at a time when there was a hemorrhagic iritis.

The lymphadenitis in this animal was also unusually marked: the photographs taken a little more than two years after inoculation show enlargement of the popliteal and the submental glands. At this time, the glands were aspirated and spirochetes were recovered.

Summarizing the work on experimental syphilis which has been presented, the points to be noted are these: First, that through a long series of observations, a number of animals with generalized lesions was collected and studied as accurately as possible with a view to gaining a more intimate knowledge of the experimental infection and through this, some clue which might lead to an explanation of the peculiar character of the infection which follows local inoculation of these animals; second, by applying the information thus acquired, we have endeavored to produce types of infection more analogous to the human disease and in this we think we have been fairly successful. How often such infections can be produced cannot as yet be stated, but from the facts which have been presented, it is evident that a generalized disease can be produced in the rabbit with a considerable degree of frequency.

Discussion.

DR. ZINSSER. I have followed this work with a great deal of pleasure, because it is one of the most systematic studies of animal disease that I have seen. Dr. Brown has obtained lesions that have never been studied with the care and systematic methods he has brought to bear on them. Some of the lesions of course have been seen before, as one cannot help finding them in studying animal syphilis. In our studies on immunity we saw keratitis, bone lesions, and knobs on the nose and occasionally on the long bones, but that was not the primary object of our study, and I have not the slightest idea what percentage of such lesions we obtained. The first reports of generalized syphilis in rabbits of which I know are those of Uhlenhuth and Mulzer, who claimed that they obtained a generalization of the organism in young rabbits. I would like to know whether Dr. Brown has observed that the youth of the rabbits has anything to do with the generalization. Dr. Brown mentioned one point that interested me particularly, and that is his idea that generalization was encouraged by the suppression of the initial lesion. This has a certain amount of direct bearing upon our work. As Dr. Brown knows we did everything we could to elucidate immunological relations by studying our strain A, both in its virulent condition, and in its culture. We tried all kinds of cross-immunization, but our immunity experiments were entirely negative, with the exception of the local immunity in recovered animals which we have published. An interesting observation which has some bearing on Dr. Brown's work is this: We did a great deal of unilateral inoculation of the testicle, and when we inoculated the opposite testis at any stage of the lesion of the first testis, the tissues of the second testis reacted as though no other inoculation had been made. By that I mean that the tissues of the opposite testis reacted just as though there had been no lesion in the rabbit.

There is another point which would seem to be of interest. For some time we were engaged in a controversy with Dr. Nichols and some others who claimed that there was a difference in the selective action of different strains of *Treponema*. Nichols described a certain strain which he obtained from the nervous system, and with that strain he claimed that he produced lesions in the testis of rabbits that differed from those obtained with other strains. We carried five different strains of spirochetes in rabbits at that time and were able to produce all the lesions described by Nichols with our own strains, and the Nichols strain produced practically all of the ordinary lesions observed with our organisms. The difference seemed to lie in the manner of inoculation. It was at that time also that Dr. Noguchi published the observation that strains of spirochetes differed in thickness and size. We studied our five strains very carefully, and found all variations in size and thickness in all of them. This point is important in that the idea of a specificity of strains and its selective action has taken hold of the clinicians and there has been a great deal written about it. Dr. Brown has had an opportunity to study these different strains in generalized lesions, and I wonder whether he has concluded that Dr. Nichols was right, or whether our observations come nearer the truth. I believe that Dr. Brown will be able to settle that question.

There is not very much more that one can say, except that, though rabbits are poor subjects for studying skin reactions of any kind, it may be worth while to try out luetin on some of these animals. The position of the luetin test is very peculiar just now, and everyone seems inclined to let it rest in peace. It is like so many things that are supposed to be settled, and then come to be doubted again. It is a thing that perhaps these chronic lesions in rabbits might give an opportunity to study. Dr. Hopkins and I made all kinds of luetin from virulent and from culture spirochetes. We could produce very potent antibodies with culture spirochetes in animals, but found that they had no action on virulent spirochetes. To make a long story short, we never found any serological cross reactions that would bring the culture spirochetes, from which the luetin was made, into any kind of serological relation with the virulent spirochete. The thing was so sharp that I have often in moments of depression wondered if the thing others as well as we have cultivated was really the *Treponema pallidum*. I cannot express such a doubt as a serious contention. It is just a thing which comes to one's mind as a bare possibility. The fact is that Dr. Noguchi, as well as we ourselves, and a considerable number of others, have found that one has to make an enormous number of plants in order to obtain a single *pallidum* culture from syphilitic material, and when the organism is once growing in the test tube, we have shown that it has completely lost its virulence, and has no serological relationship to the virulent spirochete of rabbits or man, and that the serum of syphilitic animals and man has practically no action upon the cultivated organism. This gives one a great deal to think about. It is not at all out of question, of course, that the organism in its cultural state rapidly loses its virulence, and that the virulent spirochete that we supposed at the time of doing our work, is in some way insulated against antibodies. But this matter is by no means cleared up.

DR. LAPOWSKI: May I say a few words from the clinical standpoint? Nobody can appreciate the work of Dr. Brown as much as the clinician can. I was very glad to hear his limitations. He spoke the truth, that all about syphilis is not yet known. It would be a great thing if the clinician would say the same thing. The clinician hears that the laboratory man has developed syphilis in an animal. The laboratory man shows that he obtained certain lesions which look like syphilis and which may be syphilis. But he cannot call it experimental syphilis in the rabbit, as we must first know more about non-syphilitic lesions in the rabbit. I would like to call attention to a fact that was shown in 1914 before the war; unfortunately since that time nobody has taken up the subject. In Vienna Arzt[1] examined normal rabbits and found in them mucous membrane lesions which looked like specific lesions. He found lesions on the scrotum which looked like specific lesions. He found spirochetes in the inguinal glands of the rabbit. He inoculated these spirochetes into another rabbit and obtained a lesion in the skin with *Spirochæta pallida* which could not be differentiated in the dark field from the *Treponema*, and that rabbit was never in the laboratory. Is it syphilis in the rabbit or is it something else? The question is not settled. I would like to ask Dr. Brown whether he examined the skin of the rabbits before he inoculated them, and whether he examined them in the same manner, that is, by palpation, as he says he examined the inoculated rabbits. Of course the Wassermann reaction does not mean anything in a rabbit. The next point is that Dr. Brown fortunately said you could not compare this syphilis with acquired syphilis, but with hereditary syphilis. The lesions have no analogy to acquired syphilis in man. They are rather a spirochetic septicemia. Moreover in skin diseases we have so many manifestations which look like syphilis that it is impossible for any man to make a diagnosis of one lesion and say that it is syphilis. He must have corroboration in the clinical history. I would like to ask if Dr. Brown gives us a clinical history of single rabbits. Dr. Brown is the only man who has observed inoculated rabbits for four years. I would like to know the clinical signs of syphilis in that rabbit. I believe he also had a rabbit under observation for two years. I would like to get the clinical history of syphilis in that rabbit and then you might have a picture of experimental syphilis. You cannot get it by combining the pictures from different rabbits and saying all the lesions look like syphilis. There is one more question about Dr. Zinsser's strains and Dr. Nichols's strain. Dr. Nichols's strain was a nervous strain, that it, it was taken from a spinal cord lesion and not a brain lesion. You cannot call it a nervous strain from a spinal cord lesion. A nervous strain acts differently. But you cannot make out from Dr. Brown's paper which strain is which, and in which rabbit each strain was inoculated. In order to pronounce the rabbit lesions syphilitic, you must inoculate the spirochete from the rabbit lesion into a man. It was done twice by Levaditi unsuccessfully. Nothing developed. Accidentally a man was inoculated into the dorsum of the hand during his work in the laboratory. After thirteen or twenty-eight days a papule developed. The Wassermann reaction was negative on the thirteenth day. The papule corresponded with the inoculated papule in the rabbit. Spirochetes were found in that papule, and the Wassermann reaction on the thirty-fourth day was positive, but no secondary manifestations developed. The man was watched for over six months. During this time there was only a positive Wassermann and no secondary manifestations. If you like to call a man with a positive Wasserman and no manifestations syphilitic you can do so, but that is not clinical syphilis. Another man was inoculated in the arm with the same spirochete, and they got no response. In view of these two facts, that a spirochete is present in the rabbit which cannot be distinguished from the *Spirocheta pallida*, and that inoculation was made into a man and clinical symptoms did not appear, we are still entitled to doubt whether inoculation of the rabbit, even though very successful, would be called syphilis. Surely it is not like acquired syphilis. The clinician watches the laboratory man with great expectation, but the laboratory man must adapt his paper to the clinical aspects of syphilis and pay more attention to the clinical development of experimental syphilis, to make his work of more value to the clinician, which in the end is the main object of the experimental laboratory syphilis.

---

[1] *Dermat. Ztschr.*, 1920, Feb.

Dr. Larkin: I was glad to hear Dr. Brown make the statement that he did not have anything new to offer. This work has been gone over very systematically by other workers, and his pictures are perfectly well known to some of us laboratory workers. I thought from the vast amount of work that Dr. Brown has done, and done beautifully, that he might have something to tell us when he said "generalized" syphilis in a rabbit, and that he has left fairly alone. He also has not mentioned anything about the histological details in regard to this work. He has only demonstrated to us that certain strains of spirochetes may cause experimental lesions. There is a great difference of opinion not only among pathologists, but among bacteriologists, on the different strains of *Spirochæta pallida*. Personally I have not been able to identify these different strains, although they are known as Strain "A," and so forth. But the different characteristics of the spirochetes and their relationship to experimental lesions is not known. We know perfectly well that a spirochete when injected into a testicle, removed and macerated, will produce certain lesions in the skin. The true demonstration as regards the specificity of these lesions in relation to human syphilis is not settled, so that we are not yet in a position to draw any definite conclusions from experimental spirochetal infection in animals and the same lesions which occur in human beings. I do not think that anybody has made any definite statements along that line. Those of us who have studied human syphilis for a number of years may not be so convinced when we look at those lesions in experimental syphilis in rabbits and compare them with those in the human being. I was much interested in this paper because it covers such a wide field, and it has been done in a purely scientific manner. The pictures are beautiful, and the method of presentation, and the deductions, which are very few, have been very interesting. But the lesions are very far from what we know of acquired syphilis, and those we observe in the human being are another question entirely. I was very much interested in the bone and skin lesions, but I would like to know more about generalized syphilis in the rabbit, and the changes that occur in the viscera after the generalization of the spirochete in experimental syphilis. Doubtless the field is so wide that Dr. Brown has not been able to present such questions here to-night. We have a better opportunity of seeing syphilis than any other hospital in the city of New York, because of the great system under which Dr. Fordyce works and the methods which he uses, and the conditions which he maintains in pathological examinations which are conducted under his observation. I wish to express my commendation of Dr. Brown's presentation along this line, because those of us who are interested in the diagnosis and care of syphilis know that everything along experimental lines really amounts to something when the man is intent on his work. My old friend here, Dr. Lapowski, is a perfect iconoclast when it comes to the laboratory man. At the same time he has made some very good points from his clinical experience, that the laboratory man must not stand by himself, but must help and be helped by his clinical brother.

Dr. Zinsser: May I say one more word which may avoid misunderstanding? It is possible that perhaps the two preceding speakers did not understand me correctly. I said that I was a little in doubt when I saw that the serological reactions did not show cross-relations between the culture and virulent spirochete, that perhaps we had cultivated from the rabbit the *Treponema pallidum* which was causing the lesion. I never had any doubt that the lesions which we obtained in rabbits were really lesions of syphilis.

Again, one of the speakers brought out the point that no human infection had ever taken place from rabbits. There are a number of cases of human infection on record. I saw one such infection myself in an assistant who was accidentally infected, and had the entire course, with Wassermann test, etc. The primary lesion was on the face. I have not the slightest doubt that these rabbit lesions deserve to be classified as lesions caused by the *Treponema pallidum,* and furthermore I want to make it perfectly clear that we too have found spirochetal organisms in rabbits that had no connection with the lesions. However, the other spirochetes we found in rabbits were easily distinguished from the *pallida.* Dr. Hopkins and I have published one such case.

Dr. Lapowski: Dr. Zinsser, if you have such a case it is your duty to publish it. That case would change everything. Such a statement when it comes from you should be published, in order to give other men the benefit of it, because if that is the case the whole discussion drops.

Dr. Zinsser: Well, that is the case.

Dr. Lapowski: Do you mean the case of Dr. Buschke[1] of Berlin, of a laboratory man who accidentally inoculated his finger and developed syphilis? Nobody can prove what that laboratory man did with his finger before and after inoculating it.

Dr. Zinsser: Of course I cannot absolutely guarantee that no outside opportunity for infection took place, but this point was carefully considered.

Dr. Hopkins: I would like to add a word of admiration for this work. I think that one who has worked along these lines and who knows how long it takes to get a few lesions realizes better the immense amount of labor it represents. I would also like to ask one question in regard to the regularity with which Dr. Brown has produced generalized syphilis. While we may have failed to detect some of the lesions, I do not believe that at that time, with our methods of inoculation, the same strain was as frequently producing generalized lesions as it has in Dr. Brown's hands. It seems to me that there are two possible explanations of this. One is the method of inoculation that Dr. Brown is using. The other is a possible greater adaptation of the strain for rabbits after long passage. I wonder whether Dr. Brown has tried to produce generalized lesions with a strain which has not first been carried for many years through rabbits, and whether this generalization of the disease is not a thing brought about by long passage through these animals. I recall that at one time Dr. Brown told me that he had been seeing a certain type of lesion with one strain which occurred for a while, but was not met with later on, which suggested the possibility that the strain had shifted a bit in its characteristics. It seems that that would be a possible explanation for the frequency of generalized lesions in the animals he has described.

Dr. Cornwall: I would like to ask Dr. Brown if the same lesions can be produced by inoculating the whole blood of an individual with florid syphilis as by the inoculation of spirochetal cultures. Is he able to state whether there was any difference in the frequency of histological lesions in the cential nervous system or of the occurrence of spirochete in the spinal fluid, between the Nichols's strain and strain "A"?

---

[1] *Deutsch. med. Wchnschr.,* 1913, xxxix, 1783.

DR. JOSLING: If I understand correctly, the two strains with which Dr. Brown has been working produce more general lesions now than they did when first inoculated. I would like to ask if monkeys react differently to these old strains. Such experiments might throw some light on the questions of virulence and adaptability.

DR. BROWN. There are quite a number of questions which have been raised, and there seemed to be an oversight of a fact which I mentioned at the outset, that is that the sole purpose of inciting a condition such as that described is to utilize that condition in investigating problems of human disease. Some of us would have all of this work done at once; some are interested primarily in the clinical manifestations of the infection and others in the pathology. As a matter of fact one who works in the laboratory knows that the disease under consideration is a chronic one—that it extends over months and that one person or a small group of workers cannot possibly attempt all of these problems at one time.

In regard to the publications that have thus far appeared, I think that those who are inclined to be critical of omissions should realize that the expense of the work is great and that it is necessary to condense the material as much as possible without detriment to the subject.

In reply to the question as to detailed case reports, I should like to point out that syphilis in the animal or human subject is made up of distinct entities—the case does not make the lesions but it is the combination of these various manifestations which go to make up the picture presented in the individual case. We began the publication of this work, following what we thought was an orderly procedure, taking first the individual manifestations of the infection. As I have said, such publication is expensive, and we have had to condense our material as much as possible so that we have not been able in these earlier papers to supply all of the clinical and pathological connections of the various conditions described. As you noticed in the photographs which were passed around, we have attempted to put some of these clinical manifestations together so as to make up a composite picture of the disease and eventually we shall come to a consideration of the subject from this standpoint.

We also might have gone into the histology or the pathological anatomy of the lesions but we could not attempt so much at one time. We may say, however, that we have worked up the histology of various types of lesions and that we have found no very decided difference between the histology of lesions as they occur in the rabbit, and as we find them in human beings, but they are not identical and I do not think that it is to be expected that a rabbit would react to a given stimulus in exactly the same way as a human being. This is as much as can be said and it would be futile for me to attempt to give a detailed answer to the questions which have been asked regarding the pathology of the experimental lesions.

In answer to the question of the proof of the syphilitic nature of the lesions I may say that we have not attempted to demonstrate the syphilitic nature of the infection on what one might call a clinical basis. All that we have attempted to do is to obtain a full clinical history of the lesions, to demonstrate the presence of spirochetes in the lesions, to study their histology, and from these facts arrive at a conclusion as to the nature of the condition under consideration. We have not deemed it necessary to investigate the presence or absence of spirochetes in the animal at the time of inoculation but unless the animal showed a lesion of some kind, the assumption seems warranted that the animal was at least not a highly infected one. The work of Arzt and Kerl was a very important piece of work. We have not observed conditions such as they describe and nobody knows what this organism was. The lesions produced were chiefly about the genitalia and I imagine from their description that they were quite analogous to gleet as we find it in rabbits in this country. I think one must recognize, therefore, the possibilities of confusion arising from this source in the case of certain types of lesions and look at this question with perfectly open minds. That is my attitude. Dr. Zinsser has expressed his opinion in regard to the matter of the nature of the spirochete concerned in these experimental infections and the situation may be summed up in the statement that the lesions described are produced in the experimental animal by inoculation of that animal with an organism which has presumably been obtained from cases of human syphilis.

In regard to the question of strains, we have used organisms from five different sources at one time or another; one came from the blood of a syphilitic patient with florid secondaries, another from a chancre, a third from a condyloma, Dr. Zinsser's strain came from a mucous patch, and the Nichols's strain from the cerebrospinal fluid. Whether these are distinct strains or not, I am unable to say. There may be differences in the biological properties of these organisms which are sufficient to warrant one in speaking of them as strains. As has been stated, Nichols claimed that the organism which he isolated produced certain distinctive lesions. We have carried the Nichols and the Zinsser strains through many parallel series of transfers. At first we thought that these strains were producing lesions which were different from one another, but as time has passed, the lesions have changed somewhat so that we cannot say that the lesions produced by any particular organism are more constant for that organism than for others or that the character of such lesions will be maintained through subsequent generations of transfers.

In regard to the part played by adaptation in the production of generalized lesions, we believe that both of these organisms have changed but the high incidence of generalized infections cannot be explained entirely upon the basis of adaptation. This may be seen by reference to the incidence of generalized lesions in the control animals on the chart, which gives the normal incidence following various types of inoculation, and the increase obtained by the introduction of other procedures. We have been able to produce some generalized lesions, if I may term them that, with comparatively fresh strains of *Treponema pallidum*. We have obtained lesions in the first two or three generations but since these strains were not run in large series of animals, it would be impossible to compare the results with those of the older strains. The lesions were not as numerous or pronounced, however.

Dr. Zinsser mentioned also the resistance of young as compared with old rabbits. In attempting to produce generalized syphilis, Uhlenhuth and Mulzer inoculated their animals intravenously or intracardially. Their impression was that young rabbits were less resistant to infection than the old ones. I have serious doubts of this. As far as I can see, they were giving small animals a few weeks old, a volume dose of organisms which was practically equal to that of the dose given to the largest animals; the effect was to overwhelm the young animal. Our own experience leads us to believe that it would be more difficult to obtain generalized lesions in young than in adult rabbits by using local inoculations.

Someone asked about the production of infection by the injection of human blood. It is my impression that the inoculation of blood from cases of active secondaries has given about as constant results as inoculation of material from lesions. It is not as easy, however, to transfer with the whole blood of the rabbit as it is to transfer with the material taken from the testicle, or from a skin or bone lesion.

The question Dr. Jobling raised of the alteration of the virulence of these strains for monkeys is of importance and I think the general experience has been that as organisms are transferred from monkeys to rabbits or *vice versa* they change their virulence for these animals. We are not certain, therefore, that lesions could be produced by organisms which were transferred to rabbits eight or nine years ago, but, from what we know of such conditions, the failure to infect human beings with such material would be no proof against the syphilitic nature of the animal infection.

There is another question concerning the subject of strains which may be referred to very briefly in this connection. This is one of the most important subjects in syphilis at the present time. It is claimed that there are strains of *Treponema pallidum* which will constantly produce syphilis of a certain type but as far as I am able to judge, no evidence has been submitted which shows conclusively whether these organisms differ in their biological properties, simply on account of their own life history, either in the human or animal subject or whether their biological properties are constant and fixed. In attempting to establish a nervous strain as an entity, distinct from a so-called dermatropic strain, Levaditi and Marie took a very unfortunate basis for comparison. They took a strain freshly isolated from a human source and compared the behavior of this organism with that of the old Truffi strain which had been carried in rabbits for a number of years. Their basis for differentiation rested upon the fact that there was a difference in behavior of these two organisms toward human and animal subjects. The fallacy in such work is quite obvious and I think that we will come to realize that there are many such fallacies which have crept into the work on experimental syphilis.

THE RELATION BETWEEN SPERMATOGENESIS AND LEUCOPOIESIS IN ACUTE INFECTION

HENRY E. MELENEY, M.D., AND HAROLD LINSKY, B.S.

(From the Medical Pathology Laboratory of the Presbyterian Hospital, Department of Pathology, College of Physicians and Surgeons, Columbia University, New York)

The purpose of this inquiry is to determine whether the injuries to spermatogenesis so frequently observed in acute infections, are correlated with the injury to the leucopoietic function, as manifested by absence of leucocytosis. This possibility was suggested by the well-known sensitiveness of both spermatogenic cells and leucocytes to radio-active substances and Roentgen-rays. Thirty-eight cases of acute infections in men within the period of active spermatogenesis were chosen as material. The series includes eighteen cases of lobar pneumonia, six cases of influenza, three cases of typhoid fever, and one each of lobular and bronchopneumonia, suppurative pericarditis, suppurative meningitis, suppurative lymphadenitis, acute peritonitis, acute appendicitis, and cellulitis of the forearm. The changes recorded were absence or marked decrease in the number of spermatozoa, spermatids, spermatocytes and spermatogonia, together with the presence of abnormal developmental forms and giant cells. None of the cases selected showed autolytic changes which might confuse the picture. The recent study of Mills on " The Pathological Changes in the Testes in Epidemic Pneumonia,"[1] describes the lesions in detail. Cases showing chronic testicular lesions obviously unrelated to an acute general infection were excluded.

The series is too small to justify an extended statistical treatment. Briefly, it was found that the proportion of cases showing injuries to spermatogenesis increased with the duration of the illness—a point which has already been demonstrated by Mills. The following table illustrates this relation:

---

[1] *Jour. Exper. Med.*, 1919, xxx, 505.

TABLE 1

Relation of Duration to Spermatogenesis

		Total Number of Cases	Cases With Lesions	Cases Without Lesions
One week	Cases	17	3	14
	Per cent.		18	82
Two weeks	Cases	11	4	7
	Per cent		36	64
Three weeks	Cases	6	3	3
	Per cent		50	50
Four to seven weeks	Cases	4	4	0
	Per cent.		100	0
Total		38	14	24

Not only is there a percental increase in the number of cases showing lesions, according to the duration of the illness, but the qualitative alterations increase in severity with the duration of the infection. The four cases of longest duration showed complete loss of spermatogenesis. On the other hand among the cases which have been classified as essentially normal, there were five which showed slight changes (desquamation of spermatocytes, slight decrease in spermatozoa) which may have been the beginning of more severe lesions. These cases all terminated within eight days.

It is more difficult to establish a definite correlation between leucopenia and loss of spermatogenesis. Taking the total number of eleven cases showing a leucocyte count of 10,000 or less, we find that of these, six or 55 per cent. show definite injury; whereas only eight or 30 per cent. of the twenty-seven cases with a leucocyte count above 10,000 show similar lesions of the testis. This would indicate that, disregarding other possible factors, the testicular lesions are somewhat more frequently found in the cases without leucocytosis. The apparent difference, however, is discounted when the duration factor in the two groups is taken into the reckoning. The mean duration of illness in the six cases of the leucopenic group was 14.4 days, as compared with a mean duration of 9.9 days in the twenty-seven cases of the leucocytic group. One would expect therefore a higher incidence merely on the basis of the longer mean duration of the leucopenic group.

It seems hardly worth while to elaborate further a statistical analysis of this small series of cases. It is evident from the data presented that the duration of the illness is a more significant factor in relation to the injury to spermatogenesis than the possible injury to the leucopoietic function. Certainly it is possible to state that acute infection, such as influenza, accompanied by leucopenia, is not more likely to be accompanied by injury to spermatogenesis than are other infections, like lobar pneumonia, in which a leucocytosis usually occurs.

A discussion of vitamines from various standpoints was given by Dr. Lafayette B. Mendel; no formal paper was presented.

VITAMINES AND THE AVITAMINOSES

CASIMIR FUNK, D.SC.

Whereas the chemistry of the vitamines has not materially advanced during the last seven years, the differentiation of the vitamines, proposed by us in 1912, and which included the antiberiberi, antiscorbutic and antirachitic vitamines, has been greatly substantiated by the researches made both abroad and in this country. This classification of the three types of vitamines is now accepted by all the workers and can be regarded as a definite step towards progress.

It has also been shown in the last few years, that the value of vitamines reaches beyond their importance for animal life, as it was found that vitamine-like substances play an important rôle in the metabolism of lower animals, bacterias, yeasts and higher plants. In all these new data we see a justification of the term "vitamine" applied to them, showing their importance for the life phenomena of living organisms.

If we leave certain aspects of the beriberi problem to be dealt with later, we come to the consideration of scurvy, a disease so well accepted as a deficiency disease, that it does not leave much to be discussed. Scurvy is recognized as being due to deficiency of antiscorbutic vitamine (Vitamine C). In dealing with scurvy and the value of certain antiscorbutics, we still meet with certain discrepancies. This, in our opinion, is chiefly due to the use of the guinea pig as a test animal. Let us take as an example, the protective value of fresh meat, already established for human scurvy. Tested on guinea pigs, however, the meat proved inactive. This is due to the fact that these animals require a larger quantity of C-vitamine, as compared with other animals. Harden and Zilva have found in this connection that a guinea pig of 350 gm. requires as much of that substance as a monkey of 2 kg. weight. It is altogether questionable whether we are entitled to test the value of animal foods on herbivorous animals, except when we use these foods in form of easily assimilable extracts. The question of the growth-promoting value of certain antiscorbutics has also received attention. A number of known antiscorbutics, such as orange and other fruit juices, have been found by Osborne and Mendel to contain relatively large amounts of anti-beriberi vitamine (vitamine B). Harden and Zilva have shown that from a mixture of B- and C-vitamines, the first one can be absorbed quantitatively by Fuller's earth, leaving the C-vitamine intact. According to the newest results such filtrates do not exhibit any growth-promoting power. The description of clinical scurvy in older pre-vitamine times was a good deal complicated by pathological findings in the bones, which could have been regarded as rachitic. Since the observation of Hess and Unger, who have seen rosary in cases of uncomplicated scurvy, this subject appears to be simplified to a very appreciable degree.

As regards rickets the known researches of Mellanby have substantiated our earlier contention as to the etiology of this condition. These experiments suggested strongly that rickets is due to the absence from the food of the anti-rachitic vitamine (vitamine A). We are unable to deny, however, that this view has met with a good deal of opposition; Nöel Paton considers rickets to be due to a number of causes, a view based chiefly on the old domestication theory of Kassowitz. We must, however, emphasize the fact that human avitaminoses are evidently not as simple in their etiology as the diseases which we produce experimentally in animals, in which we always endeavor (sometimes even unsuccessfully) to limit the unknown to one single factor. In clinical cases this important presumption is only rarely met with and this applies not only to rickets, but also to the other human deficiency diseases. This remark of course does not pertain to instances which are controlled in a scientific and accurate way, like the researches of Hess and Unger on human rickets, which in this case possess the convincing power of experimental research. These investigators have conducted studies of long duration on children kept on a diet, considered free from vitamine A, and who remained free from all signs of clinical rickets. Dr. Hess gave me the opportunity to see these children and I must confess that I was very much surprised to see them in such good condition. The only signs which might be of importance were a defective enamel of the teeth and a marked delay in walking, whereas a careful X-ray examination did not reveal any signs of rickets. On the other hand, Hess and Unger have seen rickets develop in children on a diet composed of whole milk, which is regarded as being particularly rich in A-vitamine. This condition cleared up on administration of cod liver oil. As the result of these studies, Hess and Unger arrived at the conclusion, that although they believe in the antirachitic properties of cod liver oil, they fail to understand how this condition can be etiologically connected with a deficiency of vitamine A. The chief reasons of these discrepancies can be seen in two factors. First of all, Mellanby, Drummond and others have shown that the requirements in vitamine A diminish with the age of the animal. Mellanby particularly emphasized the fact that quicker-growing dogs were more liable to contract rickets on a diet poor in vitamines A. It seems therefore that in the etiology of rickets, the amount of vitamines in relationship to growth impulse plays an important rôle. Now, in the experiments of Hess and Unger hereditary reasons, limiting the growth, might have played a part in their results.

A second factor, which equally deserves our attention, is the question of the content of foodstuffs in vitamine A. Whereas a few years ago the idea prevailed that only fats and oils of animal origin were carriers of this important substance, these views underwent rapid changes. Through the researches of Osborne and Mendel, McCollum and his coworkers, we know now that green leaves of plants, as well as certain seeds, contain this vitamine in relatively large amounts, whereas butter, once regarded as very rich in this substance, was found in a number of instances to carry only a moderate amount of A-vitamine. Lately it was asserted that skimmed milk, lard and certain vegetable oils contain this vitamine to an appreciable extent. It seems that the conclusions in the paper published by Macallum and myself in 1915 in which we found no difference in growth of rats, whether we used lard or butter, do not differ as much from our present conception of vitamine A, as they did then.

In view of the constantly changing conclusions as to the vitamine content of various foodstuffs, we wish to emphasize the fact, that the vitamine content is by no means a mathematical unit and that the data obtained in various laboratories in this connection can by no means be regarded as standard values, but must perforce undergo very frequent changes. It may be wrong, for example, to try to compare the vitamine value of European milk, from cows fed in post-war conditions, with milk obtainable in this country. In judging the value of a vegetable, we must not only consider the age (according to the findings of Hess), but also the time elapsed between the removal from the soil and the consumption, the climatic condition, the character of the soil and the amount of fertilizer the farmer was able to apply in each particular case. Vitamine A, according to Hopkins, is very unstable to oxidation, so that in variance with the treatment received, we can easily perceive the possibility of a butter poor in vitamine A, and lard skimmed milk, cottonseed oil containing this vitamine. It must also be borne in mind that foodstuffs found to be poor in a particular vitamine by the method of biological analysis on rats, may prove to be quite sufficient for human beings. There are even certain indications in the literature that this may be the case with vitamine A. In this light we must view the above mentioned results of Hess and Unger. By regarding the present accepted vitamine values of various foodstuffs in a critical light, we will be able to explain many of the existing apparent discrepancies in our understanding of deficiency diseases.

After these remarks, we turn to the subject which we intend to deal with to-night, namely the question of the nutritive value of animal proteins as compared with vegetable proteins, with special reference to the etiology of pellagra and hunger edema.

War edema, so frequent in Central Europe during the war, has been ascribed to almost every imaginable cause. After elimination of a number of unlikely factors, among which also the vitamine A was frequently mentioned, many investigators have arrived at the conclusion that this condition is due to deficiency of animal proteins. Kohmann, in particular, was able to produce edema in rats fed on carrots and was able to restore them to health by addition of casein. Whether or not we are justified in regarding this cure to be due to the addition of animal protein as such, we will presently see. McCarrison has found that butter and onions contain a substance which he calls anti-edema vitamine and which specifically prevents changes in suprarenals, which changes ultimately lead to occurrences of edema. During the war there was a long controversy between Hindhede and Rubner, and other German food experts, as regards the value of animal and plant proteins for nutrition. In the light of modern views on pellagra the long continued experiments of Hindhede with potatoes should have led to production of pellagra, which was not the case.

Among the views expressed on pellagra, we find the open-minded attitude of Goldberger, who stated that he was able to prevent or produce pellagra by exclusion or inclusion of foods containing animal protein. His conclusion, which we also share, is that this disease may be due to a variety of causes and possibly to a combination of a number of factors. In the English report on vitamines, which appeared in 1919, we met with the less open-minded view, that pellagra is due to ingestion of plant proteins of low biological value, with the suggestion that tryptophane may be a factor in the etiology of the disease. Chick and Hume have produced in a monkey a condition which they regard as pellagra, and which was improved upon inclusion of casein in the dietary. Whether it is logically permissible to try to produce a disease, due to lack of animal protein, in monkeys, which never have in their dietary a protein of animal origin, after they are weaned, we cannot say at present. It seems to us, that if pellagra was due to a lack of animal proteins as such, the disease should be more prevalent in countries like Russia or Poland, where the average peasant population does not consume animal proteins more than a few times a year. In spite of this fact, we see pellagra nearly limited to areas of corn consumption. The contention that whole corn is deficient in tryptophane is not borne out by experiments on birds. We can not accept the report of the British medical research committee that pellagra is due to the ingestion of biologically inferior protein.

In our researches of 1913–14 on the influence exerted by carbohydrate portion of the diet, we have observed that pigeons fed on diets containing a larger proportion of casein developed beri-beri later than those on less casein. Recently we have repeated these experiments on rats, in conjunction with Dr. Dubin. These studies, briefly stated, have shown that rats, fed on a diet containing a large amount of purified animal protein, grow on this diet on addition of a small amount of vitamine B, whereas those animals fed on diets containing a large proportion of carbohydrates required a large addition of this vitamine. So that in the presence of animal protein (plant proteins were not investigated as yet) there seems to be a sparing action, as regards requirements of animals for vitamine B and possibly also of other vitamines. It is in this light that we can view the experiments of Kohmann and of Chick and Hume on the curative effects of a casein addition. It is therefore conceivable that a diet containing a sufficient amount of vitamines may prove deficient, if the protein-content of this diet is diluted with a large amount of carbohydrates. An observation, which has not been much emphasized by laboratory workers, is the strange behavior of animals on diets containing all the necessary vitamines, but in insufficient amounts. It would seem that the animal by eating more of this food could obtain all the vitamines it needs, but in practice the reverse takes place and the animal eats less. By increasing the gross metabolism, the animal is unable to overcome the existing disproportion of food constituents. This observation alone should suffice to demonstrate the importance of the relationship of the food constituents and vitamines to each other. It is of interest to note here, that potato, in spite of the great dilution of its protein, seems to constitute a perfectly balanced food for human needs.

Now we must ask ourselves which constituent of an animal protein possesses these important properties, which we have referred to. In studying this question we have derived much information out of investigations conducted with a view of determining the nutritive requirements of certain bacterias and yeast. It would take us too long to consider all the available data and we may select a few which seem to us to be of particular interest. Lloyd, in Cambridge, working on the meningococcus, has found that this microorganism seems to require for its growth a certain vitamine (more or less analogous to B-vitamine) and a substance present in blood, which was absorbed so easily by inert material, that even filtration through ordinary filter paper had to be avoided. Williams in studying the requirements for yeast has seen that hydrolyzed casein possessed a stimulative action on yeast cells, but attributed this action to a contamination with vitamine B. Souza and McCollum have observed a similar action of hydrolyzed beef, although the presence of vitamine B was apparently excluded by experiments on rats. Finally Howard J. Mueller, in working with streptococci, has made the observation that certain hydrolyzed proteins were able to stimulate the growth of this microorganism. He endeavored to isolate the substance responsible for the above mentioned effect, which he believed to be a new unknown aminoacid. He believed this substance to be a new aminoacid for the simple reason that casein used as a starting material was carefully purified by reprecipitation before being submitted to hydrolysis. As the active substance is entirely absorbed by charcoal, it seems that the purification of casein by reprecipitation would not be the right way to free this protein from the unknown substance, as upon each successive precipitation, the condition of absorption will not differ materially from the initial precipitation. This new factor, which seems to differ from all the known aminoacids, acted very much like a vitamine, although it is conceivable that it may ultimately prove to be an aminoacid and a constituent of casein. Just how far this substance is associated with plant proteins has not been investigated as yet. We wish to suggest that this new substance, which apparently has already proved its value for the metabolism of certain bacteria and probably yeast may play a rôle in the etiology of pellagra and war edema, and may explain the contradictory evidence as regards the food value of animal and certain plant proteins. Differences in the nutritive value of proteins of animal origin were also found, in spite of the fact that their analysis did not detect any deficiency of the known aminoacids. To explain this observation, Dr. Sure recently suggested that the nutritive value of the proteins is not only dependent on their composition in aminoacids, but also on their configuration in the protein molecule, certain complexes being better utilized than others. In this way, Dr. Sure explained the nutritive inferiority of lactalbumin. The difference in the nutritive value of casein and lactalbumin may lie in the presence of the above new substance, which in the future we may be able to call vitamine D.

Discussion.

DR. PAPPENHEIMER. With whatever viewpoint one engages in the experimental study of rickets, it is necessary to take reckoning of the spontaneous occurrence of this disease in animals maintained under laboratory conditions. By "spontaneous" is meant the development of the disease under conditions that cannot as yet be accurately defined nor controlled. While such inclusive words as "domestication" and "confinement" bring one no nearer to an understanding of the pathogenesis of rickets, the observation that animals under the artificial conditions of the laboratory are prone to the disease is a very old and well established one.

Anyone who is conversant with the literature on the relation of thymectomy to the production of rickets will appreciate the justice of emphasizing this source of confusion. Now that it has become clear from the work of Renton and Robinson in England, of Nordmann in Germany, and especially the painstaking and carefully controlled work of Park and McClure in this country, that extirpation of the thymus has nothing to do with rickets, it is certain that Klose and Matti and numerous others who thought they had established a definite relation between the thymus and abnormal bone formation were misled by the spontaneous occurrence of rickets in dogs.

In rats also, rickets occurs as a spontaneous disease. Since these animals have become the favorite choice for the study of the effects of dietary deficiencies, it may be pertinent to the topic of the evening to refer briefly to some observations made a number of years ago, and already reported.

It was in connection with experiments on the possible effect of thymectomy in white rats that I had an opportunity to become familiar with the spontaneous occurrence of rickets in these animals. The work was begun in 1913, but it was not until the following spring that the disease appeared among the rats. It affected not only the operated animals but controls of the same litter, and a fair proportion of the stock animals. My interest at that time was centered in the possible relation of thymectomy to rickets, so that no control study was made of the possible dietary factors which might have influenced the development of the disease. It was frequently observed, however, that some animals of a litter became rachitic, whereas others kept in the same cages under identical dietary conditions failed to develop the disease.

There was, of course, nothing original in these observations. Morpurgo, who first described rickets in rats in 1900, studied it for many years and most accurately pictured the lesions. Such connoisseurs of rickets as Schmorl, Weichselbaum and Erdheim recognized the resemblance of rat rickets to that of human rickets and, so far as my own experience goes, I believe that the diseases are pathologically identical. It is therefore obvious that the spontaneous occurrence of the disease at times amongst laboratory rats must be kept in mind in experimental work along these lines.

I should also like to refer to one or two other isolated observations that may bear upon the subject of the evening's discussion. Through the kindness of Professor Sherman, I have had the opportunity to examine two of his rats which had been kept for some time on a diet deficient both in calcium and fat-soluble vitamines. These rats were stunted in their growth and showed at autopsy lesions which at first glance suggested rickets. There were frequent swellings of the chondro-costal junctions and at the shafts of the ribs. The bones were very fragile and broke easily. The histological study of the lesions, however, shows that they are not those of true rickets, but resemble rather the so-called pseudo-rachitic osteoporosis, which results from a deficient amount of calcium in the diet. The little swellings, which were so conspicuous in the gross, proved to be knobs of provisional callus formed about incomplete spontaneous fractures. There was great rarefaction of the cortex of the ribs with enlargement of the marrow spaces, in contrast to the excessive proliferation of osteoid tissue and the reduction of the marrow spaces which obtains in spontaneous rickets in rats.

I have one other observation which bears upon the possible relation of fat-soluble vitamine to rickets. Dr. Hess has turned over to me for study, ribs from a dog which was kept for five and a half months on one of Mellanby's rachitis producing diets. The diet consists of:

Bread	ad lib.
Krystalak	250 c.c.
Cotton seed oil	5 c.c.
Orange juice	5 c.c.
Sodium chloride	1.5 gms. daily

The histological examination of these ribs gives no indication of rachitic change. The line of ossification is perfectly regular and there is no defect in the deposition of calcium in the matrix of the cartilage or in the new formed bone. The osteoid tissue is not increased. While it is realized that one cannot draw inferences from a single experiment, one can at least say that this individual dog existed for a long time on Mellanby's diet without developing rickets.

Dr. Hess: This subject certainly is interesting a large number of medical investigators,—pathologists, biochemists, clinicians, and lately the physiologists and pharmacologists. The progress made has been very great, as one of the speakers said, when we consider that Dr. Funk wrote his book in 1914, and the amount of work that has been done since that time, and the number of difficulties that have been cleared up. On the other hand, the progress has not been entirely steady and uninterrupted. There have been points that have been very difficult to unravel for a year or more, and it is well to consider now what were the difficulties, and whether those we are meeting at the present time are not due to the same causes. Take the fact that we consider foods as chemical entities. One worker will report a result with a certain kind of food, and another worker will report quite a different result, and then after a while it will be found that the two foods are not identical. These foodstuffs cannot be considered as chemical entities. Take for example the question of dried milk. The English investigators at the Lister Institute found that dried milk had practically no anti-scorbutic efficiency. Here we found that dried milk did retain the greater part of its anti-scorbutic efficiency. This question is very clear at present. As Dr. Funk said, milk may be different initially in its anti-scorbutic content; it may be rich or poor. Then the method of desiccation makes a very great deal of difference. It will not stand a slow desiccation, but will stand a rapid desiccation. It will stand 230° F. for a half second or a second, which is the degree of heat to which it is subjected in the course of drying, but will not stand 150° or 160° for fifteen or twenty minutes. We must bear in mind that the milk may be pasteurized previous to the desiccation and condensed and finally desiccated. So there is a very good reason why one investigator will get one result and another investigator another result. It is so at the present time. One finds lard to be practically deficient in its fat-soluble vitamine content, so that it is used by Mendel as a basic diet. On the other hand, there is a recent report by Miss Daniels that if you use 28 per cent. of the lard it has enough fat-soluble vitamine to maintain rats. The same is true of cotton-seed oil. Each food product must be tested individually, and more than that, we must investigate the particular foodstuff. That is to say, lard must not be considered as lard; cotton-seed oil must not be considered as cotton-seed oil. Each different product must be tested for itself.

From the pathological standpoint there are some questions which are of particular interest, and as Dr. Mendel has said, this entire subject is one which needs the cooperation of the pathologist. In the first place, must we consider that if we get a definite pathological picture that it is due to the same etiological factor? In other words, if you get a picture in an animal or a human being of scurvy, must that be due to a lack of anti-scorbutic vitamine? Or perhaps is there something else that can produce the same pathological picture? We are used to thinking that a pathological picture means a definite disease or disorder. I bring up this question because it has been shown that a lack of the fat-soluble vitamine in the diet of guinea pigs leads to changes very much like scurvy. I have seen the tissues of guinea pigs that had had sufficient anti-scorbutic food in their dietary, that looked very much like the scurvy that I was accustomed to see when they were deprived of anti-scorbutic foodstuffs. On the other hand, there is the question whether we are in all instances dealing with a true rickets or scurvy in our experimental animals. That is another question that must be followed by the pathologists.

Dr. Funk raised the question of whether the guinea pig was a suitable experimental animal for the study of scurvy. It is, I think, too delicate a reagent. It develops scurvy so easily, so much more readily than any other animal, that we must be careful when we transfer such results directly to man. There are no doubt nutritional conditions which can be brought about in guinea pigs which would not have the same result in man. This leads to the conclusion which must always be borne in mind, namely, that after all the final test of all this work is the human being. If you get results on guinea pigs, or on rabbits, or on dogs, or on rats, or on monkeys, and they are absolutely refuted by clinical experience, we must consider whether there has not been some mistake in the experiment, not necessarily a mistake made by the investigator, but whether you can use that particular animal to elucidate the clinical condition.

I should like to say a word in regard to pellagra and rickets. In pellagra Dr. Goldberger believes that the main deficiency factor is a lack of adequate protein. For years during the war the Central Empires were deficient in adequate protein. They had practically no milk. They had very little meat and practically no eggs. In other words, they were cut off from adequate protein, and nevertheless pellagra did not develop as far as I know in Germany. When I was in Vienna this summer I asked about pellagra. They had had a few cases there. We should imagine that if this was the dominant cause that pellagra should have manifested itself in the course of the war in the Central Empires. As regards rickets, as Dr. Mendel said, Dr. Bloch of Copenhagen ascribed this keratomalacia to a lack of the fat-soluble vitamine. There was a lack of fat-soluble vitamine also in the Central Empires, and there was no keratomalacia there. On the other hand, Dr. Bloch says nothing about rickets in children, but we hear of what can be called an epidemic of rickets in the Central Empires, and no keratomalacia.

When I wrote not long ago about the relation of fat-soluble vitamine to rickets, I said not that the fat-soluble vitamine bore no relation to rickets, but that it was not the dominant factor, that there are other factors which decide whether or not it shall develop, and I am still of that opinion.

Dr. Sherman: Perhaps I might say one word about experimental diets that have been used in some of the studies of fat-soluble vitamines. In a number of cases it has been assumed that skim milk could be used in sufficient quantities to be the main source of protein and calcium of the diet, and that diets containing such quantities of skim milk would still be nearly devoid of the fat-soluble vitamine. That, I think, is a mistake. Some years ago Dr. McCollum stated that in a given amount of milk about half of the fat-soluble vitamine is in the fat-globules and about half in the watery portion of the milk. Our recent experience tends to confirm that impression, and on the basis of dry matter, that would mean that dried skim milk has somewhere in the neighborhood of half as much fat-soluble vitamine as dried whole milk. Hence the diets in which skim milk were used probably contained considerably more fat-soluble vitamine than they were regarded as containing.

The eye troubles of rats, which I think are undoubtedly characteristic of a diet lacking in fat-soluble vitamine, can be avoided or cured by skim milk practically free from fat, showing that there is a vitamine which in that respect is the same as the fat-soluble "A," and practically independent of the fat.

Dr. MacNeal: I have been very much interested in the problem of pellagra, not so much in the attempt to demonstrate that it is caused by some particular factor as in the attempt to find out, by sifting the evidence obtained by others as well as that of my own observations and those of my colleagues, what the actual cause of the disease may be. Some of the evidence which has come to light within the past year may be reviewed. Perhaps the first thing to be mentioned should be the publication by Goldberger and Wheeler of the detailed report of their work on convicts at the convict camp near Jackson, Miss., in 1915. This detailed report is somewhat different from the preliminary report, which appeared more than four years previously. From this later report it appears that the pathological condition which was produced in the convicts consisted of emaciation coupled with a dermatitis of a somewhat indefinite type, which affected the scrotum and the contiguous surfaces of the thighs; that this dermatitis, in one of the earliest cases (McD.—J. M.), itched and was relieved by bathing but later recurred. Although the authors, in their first report, designate the lesions as "typical," they avoid this term in the full report. Here they even suggest that they have some doubt about their typical character, by advancing the view that the site at least of the initial dermatitis is bound up with a specific quality of the diet and by stating that their experimental diet was probably not entirely typical of the average pellagra-producing diet.

The second point of importance is the widely recognized observation, which has been referred to by Dr. Hess, namely, that during the period of the war, when there was a remarkable deficiency in the animal protein in the dietary throughout the central part of Europe, pellagra was quite unknown. It is a disease for which some of us searched in France during 1917 and 1918 without any success whatever. If pellagra is a disease essentially due to deficiency in protein in the diet, it is rather remarkable that it should have been so conspicuously absent in those countries.

A third point of importance is the fact that pellagra did occur during the war, particularly in a large British camp for Turkish prisoners of war in Egypt. Here there were many hundreds of cases among the Turkish prisoners. Many had contracted the disease before capture and a lesser number after capture. The disease actually spread in the camp, however. It became so serious as to be made the subject of investigation by a special Committee of Enquiry. This Committee reported in December, 1918. They found a very extensive outbreak of pellagra among the Turkish prisoners, which they ascribed to a deficient diet, and they contrasted the Turkish camp with the contiguous prison camp in which German prisoners were held and in which pellagra had not appeared. The German prisoners had been living on the fat of the land before capture, and, since capture, had been receiving a diet above reproach. A most dramatic sequel has since come to light. In December, 1918, an epidemic of pellagra began in the German prison camp and a large number of cases appeared in the following six months. Thus, almost at the moment that the dietary experts had pronounced the diet above reproach and had ascribed the absence of pellagra to the excellence of this diet, the epidemic started. Enright, who has reported this outbreak in the *Lancet*, draws the conclusion that he has disproved the relationship of diet as the sole causative factor of pellagra. I think that this very dramatic demonstration has served to change the whole aspect of the pellagra problem as far as the English investigators are concerned.

Evidence pointing to this same conclusion has been furnished long since by American investigators of pellagra and the pellagra situation in this country will still bear further investigation in the light of these developments of the present year.

Dr. Haas: All those who have spoken to-night have called attention to the fact that this is not a straightforward, clear-cut proposition; that the facts in some respects are proven and definite, but they are isolated facts. It is really a matter for regret that so much lay publicity should have been given to a subject of such importance, in which such excellent work is being done. Mention has been made of disturbing factors in the investigations due to the character and quality of the foodstuffs themselves. No mention, however, has been made of the individual reaction of the animal. Recently I was able to show that at least in the human infant a very definite reaction with consequent growth may be produced by relatively minute doses of atropin, supposedly due to its action on the sympathetic system. The undergrowth of cretinism and the overgrowth of dyspituitarism are too well known to need mention. Herter some years ago called attention to the infantilism which might be the result of a special type of intestinal flora; and so in discussing this problem we are discussing a many-phased subject, and one which in its application to human pathology must be proceeded with very carefully. Take for instance the tomato. It has been fairly well proven to be a satisfactory anti-scorbutic, yet one of the worst cases of scurvy I have seen lately has been fed tomato daily for many months. And so one might go down the list.

The problems of nutrition are so involved and obscure that the greatest caution is necessary in translating laboratory experience to clinical application.

Dr. Jobling: My experience with pellagra in the South makes it impossible for me to accept the theory that this disease is due solely to a dietary deficiency. Particularly does this apply to a deficiency of what some English writers term "biological protein," as I know of instances in which pellagrins have been consuming a very liberal diet previous to the onset of the disease. I have made repeated inquiries concerning this disease of a number of old Southern surgeons, men who were connected with the Confederate armies, and have yet to hear that any of these men, during this period, observed cases of what we now recognize as pellagra. To those who are familiar with the diet of the Southern soldiers during this period this would seem rather strong evidence against the idea that it is due to a deficiency of protein, as their diet in many instances, and for long periods of time, consisted to a large degree of parched corn. Again, if this is true, why should we have had the outbreak of the disease during the period extending from 1910-1914, after which it declined? Are we to assume that the people of the Southern States acquired a hatred for protein substances at this time, and then returned to their former diet? If it is due to a lack of protein, the disease should be very prevalent in Austria, and apparently such is not the case.

Dr. Funk: Workers in this field know that all dietary deficiencies are not necessarily of a vitamine nature and therefore we hardly need to stress this point further. However, we are of the opinion that other fields of nutrition will benefit by the results of vitamine research. We have in mind particularly the chemistry of the proteins and the study of their nutritive value; here, vitamine research will apparently provide us with new ideas that have been lacking in the last ten years.

We have followed closely the literature on the cattle diseases in South Africa, mentioned by Dr. Mendel. These investigations passed through the various stages typical of a disease whose etiology is unknown, and was finally attributed to a deficiency of phosphorus. This pertains to "lamziekte," but there are other diseases in the same territory, one called "stijfziekte" (apparently analogous to rickets) and another called "poverty." A simultaneous occurrence of diseases, which may be regarded as deficiency diseases, together with a deficiency of phosphorus in the plants, suggests that there might easily be a lack of some other food constituents in the fodder.

We should not be discouraged by the apparently insurmountable difficulties that have been mentioned to-night. Definite progress has been made and whereas a few years ago it was thought that there was nothing further to be known about vitamines, we are at present aware of the fact that we must settle down to real work if all the intricacies of the problem are to be untangled. We must have more constructive and less destructive work.

BESREDKA'S METHOD OF ORAL IMMUNIZATION OF RABBITS WITH OX-BILE AND PARA-TYPHOID VACCINE

ABRAHAM ZINGHER, M.D., AND DAVID SOLETSKY, M.D.

During the past two years Besredka (1–5) reported from the Pasteur Institute an interesting series of experiments on a method of active immunization of rabbits against the Shiga dysentery, typhoid and para-typhoid B bacillus. This method consists in giving *per os* one dose of a vaccine which has been prepared by heating at 60° C. for one hour a suspension of bacteria grown on agar slants. The principle of this method, according to Besredka, does not depend upon a general immunization of the entire body, but upon the establishment of a local resistance or, as he terms it, impermeability of the intestinal wall. For this purpose the intestinal mucosa has to be partly denuded so as to bring the solitary lymph follicles of the intestinal wall into close contact with the vaccine. With the Shiga dysentery the vaccine alone is sufficient both to denude the mucous membrane and later to render the intestinal wall impermeable to its toxin and endotoxin. In the case of typhoid and paratyphoid vaccines, however, the intestinal mucosa has to be first prepared by administering to rabbits *per os* on the previous day from 8 to 10 c.c. of ox-bile that has been mixed with some licorice powder. The animals are kept without food until the following morning, when they receive a second similar dose of ox-bile, and two hours later the vaccine through a small catheter.

According to Besredka, this method of vaccination results in establishing an impermeability of the intestinal wall to the living organisms and an insusceptibility of the cells to their endo-toxins, which makes the animals resistant to the infection. Such an infection can be produced in normal rabbits by giving them *per os* bile and a large dose of living bacteria. To obtain uniform results, however, he injected a fatal dose (for the unprepared rabbit) of the living bacteria *intravenously* after preparing the rabbits with bile in the manner described above. After a fatal intravenous injection with the paratyphoid B bacillus, the autopsy shows marked congestion of the intestines, and especially of the Peyer's patches, engorgement of the mesenteric vessels, and a very characteristic muco-purulent inflammation of the gall bladder, the wall of which is thickened and studded on its surface with numerous whitish points. Cultures from the contents of the gall bladder and the small intestines show an abundant and sometimes almost pure growth of the paratyphoid B bacillus. The vaccinated rabbits when tested for immunity are not affected by the intravenous injection of the same dose of the organisms.

To prove that the impermeability of the intestinal wall is the important factor in this form of immunity, Besredka administered *per os* to rabbits that had been prepared with bile a sub-lethal dose of paratyphoid B. bacilli. The agglutinin titer and the serum content in protective substances rose rapidly and reached their height about the twenty-fifth day. On that day the agglutinin content varied from 1:20,000 to 1:80,000 in different animals. At the end of two months the agglutinins were found to be rapidly diminishing. The ingestion at this time of a second dose of living bacteria plus bile did not result in a second increase in the agglutinins and protective substances. On the contrary, the agglutinins two months later were found to have dropped to from 1 : 200 to 1 : 400. Besredka assumed therefore that the first ingestion of the living bacteria produced an impermeability of the intestinal wall, which prevented the living bacteria and their endo-toxin given with the second dose from passing through into the general circulation and causing the formation of immune bodies.

A third factor of interest was shown by the author that the intravenous dose necessary to produce a fatal infection with the paratyphoid B. bacillus in rabbits prepared with bile was only about one tenth of the amount necessary to produce a similar infection in rabbits not so prepared.

To verify these important findings of Besredka we commenced our work by attempting to immunize rabbits with a vaccine prepared from the paratyphoid B. bacillus. The greater practical importance of typhoid and paratyphoid vaccination and the more detailed communication of the author on the use of the paratyphoid vaccine induced us to start our work with this organism.

The culture of the paratyphoid B. bacillus used in our experiments was a strain isolated several years ago in one of the army camps in this country from a case of paratyphoid fever. The vaccine was prepared by growing the bacteria on agar in pint Blake bottles at 37.5° C. for twenty-four hours and heating the suspensions to 60° C. for one hour. Several lots of vaccines were prepared. In some of the experiments a fresh lot of vaccine was used, and in others vaccine that had been kept in the ice box for a maximum of four to six weeks. No difference in results was noted between fresh and preserved vaccine. One dose of vaccine was given except in the case of two rabbits, which received three doses. The multiple doses gave the same result as the single dose. The vaccine was introduced into the stomach through a small catheter.

A standard slant culture was adopted. The test tubes used had an inside diameter of 18 mm., and the slant surface of agar a length of 50 mm. The culture was grown for twenty-four hours at 37.5° C.

The bile used in most of the experiments was fresh ox-bile that had been passed through a bacteria-proof filter and kept in the ice box until used. Some of the experiments were made with fresh bile that had not been passed through the filter, but no difference was noted in results. The bile was injected into the stomach through a small catheter in order to make certain that the animal received the entire amount (8 to 10 c.c.) with each dose. The routine consisted in giving the first dose of bile during the latter part of the afternoon and keeping the animals without food until the following morning, when they received the second dose of bile. Food was again withheld, and two hours later the vaccine was injected through a catheter. The animals were then allowed to feed as usual.

Group I. Animals Prepared with Bile, Receiving Living Bacteria Intravenously to Determine the Fatal Dose: A series of ten rabbits was injected intravenously with living bacteria in doses varying from one-fiftieth of a slant to one-fifth of a slant. The animals were prepared with bile as described above.

All six animals that received from one fiftieth to one tenth of a slant died at intervals varying from two and a half to twenty-three days. In each case the autopsy showed typical lesions of paratyphoid infection as described above. Pure cultures were obtained from the diseased gall bladder and almost pure cultures from the small intestine. The remaining four rabbits received doses of one-tenth to one-fifth of a slant. These animals died acutely in two to four hours, showing an acute diarrhoea and rapidly increasing muscular weakness. The autopsy was negative with the exception of a general engorgement of the vessels of the mesentery. The dose used in our experiments in testing the vaccinated rabbits for immunity varied from one twenty-fifth to one-eighth of a slant.

Group II. Animals not Prepared with Bile Receiving Living Bacteria Intravenously. There were eight rabbits in this group. The animals were injected intravenously with a dose varying from one one-hundredth of a slant to a full slant. Five animals receiving doses varying from one one-hundredth to one-third of a slant survived the injection. The animals receiving one-half a slant and one full slant died at intervals varying from one and a half to three days. The autopsies in these rabbits showed a typical paratyphoid infection. It is apparent that the intravenous dose necessary to produce a fatal infection in rabbits prepared with bile is reduced to about one-tenth of the amount that has to be given when the rabbits are not thus prepared. In this respect we were able to obtain results which corresponded closely to those noted by Besredka.

Group III. Animals not Prepared with Bile Receiving Killed Vaccine Intravenously: We thought it advisable to test the toxicity of a killed vaccine by injecting it intravenously in rabbits that were not prepared with bile. The animals died quite promptly in from two to twenty hours. One-half slant produced an acute diarrhœa, marked muscular weakness and death in two to four hours. One-third slant killed the animals in six to twenty hours.

The intravenous injection of the supernatant fluid obtained by centrifuging freshly prepared vaccine in a dose corresponding to the washings of a half agar slant killed animals acutely in three hours. The endo-toxins liberated from the bacteria present in this fluid produced symptoms closely resembling the ones noted in vaccinated rabbits tested for immunity with bile *per os* and a much smaller dose of the living bacteria intravenously.

Group IV. Animals Receiving Killed Vaccine per Os: Eight rabbits received vaccine plus bile. The heated vaccine was given in a dose corresponding to one fourth of the growth on a pint Blake bottle. Agglutinin tests at weekly intervals made during the following five weeks gave negative results. Four of the eight animals were tested for immunity at the end of three weeks by preparing them first with bile and then injecting them intravenously with a fatal dose of the paratyphoid B. bacillus. None of the animals showed any immunity, three of the rabbits dying even more rapidly than the normal controls.

Three rabbits received vaccine alone without bile. Here we expected no immunity, as Besredka had stated that preparation with bile was essential in producing local resistance of the intestinal wall. No agglutinins were found in subsequent bleedings. When tested for immunity from three weeks to two months later the animals succumbed in from two hours to four days.

Group V. Animals Receiving Living Bacteria per Os: Four rabbits were prepared with bile and received living bacteria in a single dose varying from one-fourth to a full surface culture from a pint Blake bottle. The suspension of the living bacteria was injected through a small catheter. Agglutination tests in dilutions of 1 : 50, 1 : 100, and 1 : 200 at weekly intervals during the following four weeks gave negative results. Three of these animals were subsequently tested for immunity, two at three weeks and one at six weeks after receiving the living bacteria *per os.* Two of the rabbits died rather promptly and one survived. This animal had been tested with one-fifteenth of a slant and was re-tested two months later with a larger dose—one eighth of a slant. The animal died at the end of five days, the autopsy showing the typical picture of paratyphoid infection.

Three rabbits that had not been prepared with bile also received living bacteria *per os.* In this group we expected to find no immunity. One animal died of an intercurrent infection, the two surviving ones were later tested for immunity with negative results.

Conclusions

1. No immunity was obtained in rabbits prepared with ox-bile and given living or dead paratyphoid B. bacilli *per os.*

2. No agglutinin production was noted in rabbits receiving living or dead bacilli *per os* either with or without bile.

3. The intravenous fatal dose of paratyphoid B. for rabbits prepared with bile was only about one-tenth of the amount required to produce a fatal infection in rabbits which were not so prepared.

4. The killed vaccine of the paratyphoid B. is more toxic than the suspension of living bacteria.

Bibliography

1. Besredka, A.: *Comp. rend. Acad. d. sc.*, Par., 1918, clxvii, 212–214.
2. Besredka, A.: *Ann. d. l'Inst. Pasteur,* Par., 1919, xxxiii, 301–317.
3. Besredka, A.: *Ann. d. l'Inst. Pasteur,* Par., 1919, xxxiii, 557–568.
4. Besredka, A.: *Ann. d. l'Inst. Pasteur,* Par., 1919, xxxiii, 882–903.
5. Besredka, A.: *Bull. d. l'Inst. Pasteur,* Par., 1920, xviii, 121–129.

Discussion:

Dr. Huntoon: I must confess that I am disappointed. I came miles to learn the successful technique, and now Dr. Zingher tells us that it cannot be done. This paper of Besredka's of course awakened everyone on the subject of immunization, because it takes up the whole question of what immunity is. There is some evidence, more or less scattered, that the resistance of an animal to infection really resides in the cell. Some years ago Dr. Elser and myself fed rabbits typhoid bacilli, living, but put in capsules. I remember feeding the rabbits the capsules every morning. Then we tested the rabbits' blood weekly for agglutinins. We found nothing until one rabbit developed apparently a spontaneous diarrhea, promptly followed by the appearance of agglutinins in the blood. We could not isolate typhoid bacilli from the stool. We took the other rabbits and injected them intravenously with killed meningococci because we knew that this caused lesions to appear in the intestinal wall. Very promptly agglutinins for typhoid appeared in the blood. We found that they were common agglutinins for typhoid, colon and para-typhoid. I would like to ask Dr. Zingher if he used para-typhoid B. If so, that would account for the early deaths with the larger doses.

Dr. Ewing: I think it would have been of interest for Dr. Zingher to have determined whether the administration of bile did actually denude the epithelium. I think this point deserves proof. Did Besredka put the bile through a Berkefeld filter?

Dr. Zingher: We used one specimen of bile that had been passed through the Berkefeld filter for most of our experimental work, as we wanted to avoid variations due to different specimens. However, we also used in some of our experiments fresh unfiltered bile with no difference in result. There is no statement in Besredka's communications whether or not he had passed the bile through a filter. In regard to Dr. Ewing's first question, this would no doubt be an interesting fact to determine. The point at issue however was the ultimate result, whether the rabbits did or did not develop an immunity when they were first prepared with bile and then given the killed vaccines by mouth. If results had been satisfactory, then a closer study of the pathology would have been made.

Dr. Huntoon: I would like to see the rabbits treated with calomel in place of the bile.

Dr. Jobling: I am afraid I do not understand just why you should attempt to remove the epithelium when you can give it intravenously.

Dr. Zingher: Besredka states that the only immunizing effect after an intravenous injection of vaccine results from the small amount that actually comes in contact through the circulation with the intestinal wall. The administration of vaccine *per os* has ordinarily no immunizing effect, but by denuding the intestinal epithelium with bile Besredka believes that the vaccine is brought into intimate contact with the solitary lymph follicles of the intestinal wall, and this contact action produces an impermeability of the intestine to the living bacteria of their endo-toxin.

Dr. Huntoon: Besredka tried to prove that there is a difference between humoral and tissue immunity.

Dr. Zingher: Besredka claims to have shown in his experiments that a general immunity as indicated by the presence of antibodies such as protective substances and agglutinins is of relatively little or no importance in protecting the individual against these intestinal infections. According to him, the local resistance of the intestinal wall is the most important factor. An interesting phase of intestinal immunity that develops during the latter part of the disease and during the early convalescence from the intestinal infections of the typhoid-dysentery group was recently discussed by Bordet before the Johns Hopkins Medical Society. I refer to the bacteriophage reaction of D'Herelle. According to D'Herelle we are dealing with a filterable virus which is present in the intestinal contents of patients suffering from various infections of the typhoid-dysentery group. This virus increases in amount as the patient progresses towards convalescence. A small amount of the Berkefeld filtrate of the stool which has been diluted with bouillon added to a fresh culture of the organism producing the infection will cause lysis and inhibition of the growth of the bacteria. When the bacteriophage is very active, the lytic broth culture planted on agar slants will show no growth. When less active there will be seen on the surface of the agar slant small circular depressed areas surrounded by a good growth of the culture of the organism. These depressions are supposed to be colonies of the invisible microbe. Bordet has obtained the same lytic exudate from the peritoneal cavity of guinea pigs which have been injected with a few doses of *B. coli*.

Dr. Cornwall: This is not exactly apropos of the discussion. We know of course that typhoid vaccine has not been successful in protecting individuals under all circumstances against typhoid fever. While in France I had an opportunity to observe a small typhoid epidemic of some twenty-two cases, six of whom died. They had all been immunized at varying times with U. S. Army vaccine. In all of the six cases the intestinal lesions extended high in the duodenum, being within six inches of the pylorus in two instances. The gross examination suggested a greater immunity in the upper intestines, as the lesions became more extensive in the lower intestines. In some instances the duodenal lesions were completely healed, presenting the typical shaven beard appearance. In all of these cases there was a definite interstitial pancreatitis. So far as any autopsies I have seen, or reports I have read, it is not my impression that interstitial pancreatitis is an ordinary accompaniment of typhoid fever. These lesions extend much higher than the lesions of typhoid I have been accustomed to see in New York. The lesions in the upper intestines would seem to have been taken care of pretty well. One case that died showed that the lesions in the duodenum, jejunum, and upper ileum were all very well healed, and there were just two or three active lesions very low down. It looked as if the man should have gone on to convalescence. I should like to ask, if, in the experience of those present, interstitial pancreatitis has been observed as a frequent accompaniment of typhoid fever.

Dr. Zingher: Besredka's statement with regard to the incidence of typhoid fever in the French Army does not correspond entirely to the results published by Major Edouard Riis on the same subject. The latter showed that the incidence of typhoid and para-typhoid fever was considerable in the French Army during the first year of the war when the mobilization was so rapid that anti-typhoid vaccination could not be carried out. But just as soon as the French authorities started to vaccinate their troops with typhoid vaccine, the incidence of this disease was greatly diminished, while that of para-typhoid remained unchanged. The triple typhoid vaccine finally used consisting of typhoid and the para-typhoid strains reduced the incidence of these diseases in the French Army to a very low percentage. One must also remember our own experience with typhoid vaccination in the American Army. Some of the soldiers who developed typhoid later had received only an incomplete series of triple typhoid injections, or no vaccine at all. These soldiers in one way or another avoided the injection of the vaccine, and thought that they were getting the best of the Army surgeons.

QUIESCENT METASTATIC GASTRIC CARCINOMA

G. L. ROHDENBURG, M.D.

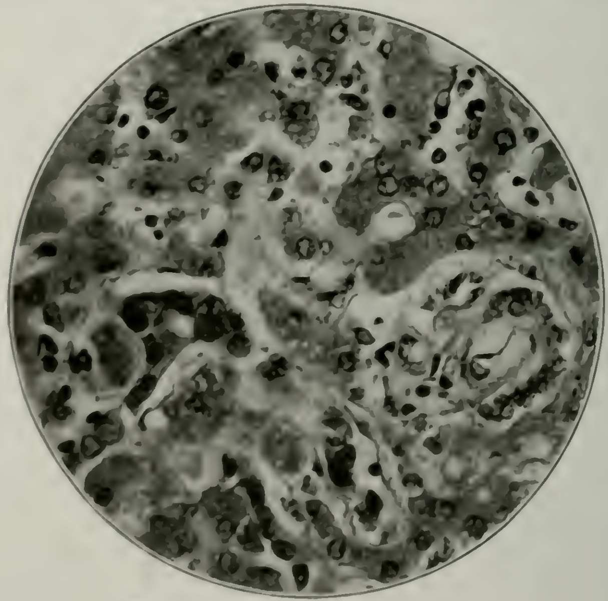
(From the Pathological Laboratory of the Lenox Hill Hospital, New York City)

This case is of interest from the standpoint of immunity in cancer.

The patient, a German, male, aged fifty-three, was admitted to the hospital complaining of weakness and fever. His past history was uneventful except for the fact that he very definitely asserted that ten years previously he had been operated upon for a malignant stenosis of the pylorus. He was in the hospital for a period of two months, eventually dying of pulmonary edema. Physical examination showed the following: a lemon yellow color, no cardiac murmur, evidences of a probably healed tuberculosis of both apices, and a slightly enlarged spleen. Two days before his death fluid was demonstrable in both pleural cavities, and a sudden shower of petechiæ appeared on the abdomen and inner aspects of both forearms and thighs. The radiographic examination showed a patent gastroenterostomy, but gave no evidence of a pylorus or duodenal cap. His blood counts showed a leukopenia with a slight lymphocytosis; his red cell count had all the characteristics of an anemia of the pernicious type. His urine showed a faint trace of albumin with an occasional cast. All other laboratory examinations were negative. During his stay in the hospital he had a fever of a septic type ranging between the normal and 103° F.

The cardinal points demonstrable at autopsy were a double sided hydrothorax, fresh small vegetations on the middle leaf of both the mitral and aortic valves, a healed and calcified tuberculosis involving both apices, parenchymatous degeneration of the liver, an acute splenic tumor with a recent infarct in the upper pole, and a mild degree of chronic nephritis.

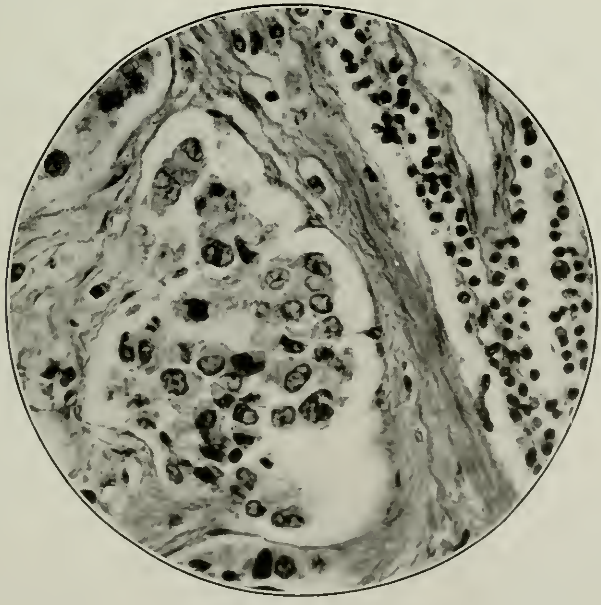
The findings which are of interest in the present connection were those of the gastrointestinal tract. The pylorus and a portion of the descending duodenum were absent, and the stomach was bound to the liver by a band of dense adhesions. At about the middle of the stomach there was a posterior gastroenterostomy with the first portion of the jejunum. In the mesentery of the jejunum there were about thirty-five hard white nodules varying from 0.25 to 1 cm. in diameter. On section these masses were very firm and had the gross appearance of fibroids, and they were distinctly different in appearance from the pink soft mesenteric lymph glands. These



Quiescent carcinoma cells in liver.

masses on microscopical examination showed polymorphous cells with large nuclei and dense protoplasm arranged in a variety of ways, some being in broad sheets, others in strands, and still others in alveoli. Supporting these cells was a dense hyaline trabeculated connective tissue in which were collections of lymphoid cells having the architecture of lymph gland germinal centers. The condition is well shown in the accompanying photographs.

Several years ago in making a summary of the reported cases of spontaneous recession of human malignant tumors it was pointed out that such occurrences were not quite as rare as is commonly supposed. It is the experience of most surgeons and pathologists to have encountered cases of neoplasia in which there is a recrudescence at an unusually late interval, thus we have recently seen a breast carcinoma which developed a metastasis twenty-three years after the breast amputation. That neoplastic cells with their well-known power of almost limitless growth should remain quiescent for such long periods seems almost unbelievable, but as the present case shows such an occurrence is possible. The observation and recording of cases of this type are of extreme importance, for such cases demonstrate that at times



Quiescent carcinoma nest in mesenteric lymph-node.

nature can control the process, and what nature can do, man will eventually be able to duplicate, even though the present outlook is pessimistic in the extreme. In conclusion we would urge the necessity for a very careful inspection of all cases coming to autopsy at any considerable period after the removal of a neoplasm, particularly where death has resulted from a noncancerous condition. An analysis of many cases of this type may possibly lead to therapeutic measures which will prove to be of great value.

Discussion

Dr. Wood: I have seen a number of cases of carcinoma of the breast which after operation have had recurrence either in the scar or the supraclavicular nodes at the end of from five to fifteen years, and in which the morphology of the tumor was that of the primary growth, as the original sections were in my collection at St. Luke's for comparison. This case of Dr. Rohdenburg's is however much more interesting than any of mine, because it is more exceptional, as the late recurrences of a breast carcinoma are well known. It is not necessary to speak of the folly of reporting cases of neoplasm as cured in six months before this audience and in the presence of this interesting report, yet the current literature is full of them. We have to be still more cautious with x-ray and radium reports, because all of our animal experiments show that the cells after large doses of radiation are slowed in their growth, and a tumor which would normally recur in one week does not return for six or seven weeks. This corresponds to years in man. That a similar slowing may occur in human material is shown by the fact that there have been a number of cases reported of recurrence eight or nine years after an apparent cure of the tumor by x-ray. One patient whom I saw went nine years without symptoms after treatment of an epithelioma of the lip, and then developed a recurrence in the neck, so that much discretion should be used in talking about the cure of a carcinoma.

METASTASIS OF CARCINOMA INTO AN ENDOTHELIOMA OF THE OPTIC SHEATH

MARTIN COHEN, M.D., AND WARD J. MACNEAL, M.D.

(*From the Department of Ophthalmology and the Department of the Laboratories, New York Post-Graduate Medical School and Hospital*)

Abstract[1]

History and Clinical Features: Mrs. J., aged 45, was admitted to Harlem Hospital on March 26, 1920, with a diagnosis of carcinoma of the brain. The left eye has been practically blind since about October, 1917. Vision in the right eye had been good until the last three months. The left breast had been removed for carcinoma in December, 1918. The important clinical features were: (1) practical loss of vision (light perception only) in the left eye, of long duration, associated with only moderate dilatation of the pupil, sluggish response to light, slight temporal pallor of the disc and absence of vascular changes in the retina; (2) temporal pallor of the left disc; and (3) unilateral papilloedema of the right disc with reduction of vision to perception of movement of fingers at one meter. The patient died eight days after admission.

Necropsy: This was limited to the cranium. The cerebral convolutions were flattened. Surrounding and adherent to the intra-cranial portion of the left optic nerve was a rounded tumor about 3 cm. in diameter. The left optic nerve was elongated and distorted by the tumor and the optic chiasm was displaced to the right. Cut surface of the tumor appeared white and homogeneous. Upon sectioning the brain several separate tumor nodules were found in various parts of its substance.

Microscopic Examination: Sections of the cerebral metastases show infiltrating new growth, consisting of large cells arranged in solid masses, as narrow columns and sometimes as tubules. The nuclei are large and mitotic figures are frequent. These tumors are regarded as secondary carcinomata from the primary growth in the breast.

Sections of the rounded tumor at the left optic foramen show a mixed character. In general it consists of irregular whorls of densely packed, elongated or spindle cells separated by somewhat looser connective tissue. Small hyaline bodies with concentric markings and deposits of lime salts are present in very small numbers. At one place the lumen of a large vein contains a mass of the new growth projecting from the wall into the lumen. These general features characterize the tumor as a dural endothelioma.

This new growth was readily separated from the neighboring structures, with the exception of the left optic nerve and its sheath. This nerve is

---

[1] The full paper, with illustrations, will appear in the *Archives of Ophthalmology*, 1921, Vol. 50, p. 128–136.

surrounded by the tumor at the inner termination of the optic foramen and considerably distorted. Sections show the intracanalicular portion of the intervaginal space occupied by the endothelioma, which does not pierce the pial sheath but appears continuous with the inner layer of the dural sheath and the outer layer of the pial sheath. The tumor has evidently taken origin from the layer of cells lining the intervaginal space in the intracanalicular portion of the optic sheath, it has compressed the nerve in this region and has extended backward in the intervaginal space to the cranial cavity, where it has enlarged to form the visible irregularly rounded mass in the subarachnoid space.

Mallory has somewhat recently studied the type cells of these tumors and he would place them in a new class designated as arachnoid fibroblastoma. He considers the lining of the subarachnoid space, from which these tumors are derived, to be merely a differentiated connective tissue, rather than endothelium.

Within the sections of this endothelioma (arachnoid fibroblastoma) are found groups of cells of a quite different type. These occur in the inferior and mesial portion of the tumor. They appear to correspond in all respects with the type of cell in the cerebral metastases and many of these cells show mitotic division figures. There is here, evidently, a metastatic carcinoma of recent development invading the basal portion of a dural endothelioma of longer standing.

Pathological alterations have not been demonstrated in the sections of the right optic nerve. The left optic nerve, on the other hand, was distorted and compressed near its entrance into the cranial cavity and the intervaginal space filled up with new growth in the inner half of the intracanalicular portion. This new growth is endothelioma containing nests of carcinoma. The cross section at the intracranial end of this nerve shows extensive degeneration of the nerve, doubtless brought about by the pressure upon the nerve within the optic foramen. Cross section of the nerve at the posterior orbital portion shows the myelin fairly well preserved for the most part, but there is a somewhat indefinitely outlined crescentic light patch of degeneration in the temporal half of the nerve, which evidently corresponds to the situation of the more delicate papillo-macular bundle of fibers.

Summary: The anatomical points of interest may be enumerated as follows: (1) multiple metastatic carcinoma of the cerebral substance; (2) large dural endothelioma (arachnoid fibroblastoma), arising in the intervaginal space in the intracanalicular portion of the left optic sheath, compressing and distorting the nerve and extending backward to expand into a large rounded mass in the intracranial subarachnoid space; its pedicle and inferior portion being infiltrated also by metastatic carcinoma; (3) extensive degeneration of the intracranial portion of the left optic nerve associated with rather limited degeneration of the posterior orbital segment, the latter confined to the papillomacular region of the nerve.

Bibliography

Byers, W. G. M.: The Primary Intradural Tumors of the Optic Nerve: Fibromatosis nervi optici. Studies from the Royal Victoria Hospital, Montreal, August, 1901, Vol. 1, pages 1–82.

Mallory, F. B.: The Type Cell of the So-called Dural Endothelioma. *Jour. Med. Research*, 1920, xli, 349–364.

Discussion:

Dr. Larkin: In looking over the sections of the tumor I observed something that I have never seen before in a brain tumor. The tumor belongs to that type seen frequently in the meninges, single or multiple endothelioma. These tumors have a typical morphology and a typical histology. In looking over these sections there is evident a mixture with a different tumor type; there is carcinoma mixed with endothelioma. It is rather convincingly shown in sections given me that an endothelioma has metastasized into a blood vessel. This is worthy of note. There are three histological types of tumor in this brain; one is an endothelioma which is perfectly characteristic histologically; the other is an admixture of endothelioma with carcinoma, the carcinoma arising as a metastasis from the breast, and there is a different type of tumor which I do not believe Dr. MacNeal has shown on the slide. It is a peripheral arrangement of cells closely packed around the blood vessels scattered here and there in the brain substance, so that the pictures show an endothelioma, a carcinoma, and a whorl-like arrangement of an endothelioma.

Dr. MacNeal: If I understood Dr. Larkin correctly, he regards the material inside the blood vessels as a third type of tumor, or as indicating a tendency on the part of the cells of the endothelioma which is not commonly observed. The reports of this type of tumor are not very abundant, but the most careful study seems to be that of Mallory, and he calls attention to the fact that the cells of the arachnoid have a normal tendency to form groups of cells, which are anatomically known as arachnoid villi, which under normal conditions extend into the blood vessels. The extension of these cells into the blood vessel does not justify one in assuming that a metastasis is being set up, for we must remember that the structure resembles a perfectly normal structure. A tendency to produce structures similar to the normal is observed in many of the benign tumors. My interpretation here may of course be incorrect, but I would say that we have in this particular picture something which resembles more or less accurately the formation of an arachnoidal villus growing into a vein. It does correspond very accurately indeed with a perfectly normal arachnoidal villus in a child five years old, as shown in one of the figures of Mallory's paper. I do not believe that you can assume that there is a metastasis here merely because of this villus growing into the vein. It would be necessary to demonstrate the presence of secondary tumors of this type separate from the primary endothelioma. I cannot convince myself that we have anything in the brain substance which corresponds to the arachnoid fibroblastoma (endothelioma). All the other tumors found in the pituitary body and in the brain substance seemed to correspond with the second type of tumor, the carcinoma, and not to the fibroblastoma or endothelioma. That is my interpretation of the thing.

Dr. Larkin: The histology of this tumor differs from the appearance which I have seen in other endotheliomata of the dura. There is no question as to the nature of the metastatic masses which point into the veins in different parts of the endothelial tumors. The histological type of metastasizing mass into the vein corresponds exactly to the type of tumor outside, that is, there are the whorls which are in the vein itself, and these whorls are similar to the cell type found outside the vein in the tumor itself. Mixed up in the mass of tumor tissue outside of the vein are secondary tumors derived from the carcinoma of the breast. I think this is an unusual picture of metastatic involvement so interesting histologically that it is worthy of record.

Dr MacNeal: I am not sure yet that I comprehend the point Dr. Larkin has in mind. I agree perfectly that the villus is a growth inside the blood-vessel, and that it is similar in structure to the arachnoid fibroblastoma outside of the vessel in that particular tumor, but when you transfer your attention to the metastases I cannot see anything which corresponds to the arachnoid fibroblastoma. If there are sections showing this relationship I have not seen them, and I would be very glad to do so. I have not been able to find any such structure at a distance from the original large rounded tumor, and it seems to me that proof of metastasis must rest on such a finding.

Dr Larkin: There is no question that we have two different types of tumors growing in the brain.

Dr. MacNeal. I have not been able to satisfy myself of that. The large tumor was not in the brain. It was in the sub-arachnoid space.

Dr. Larkin: I have some sections you gave me of two different types of tumor, one an endothelioma with an admixture of carcinoma, and another tumor which is perithelial in type. Histologically there is an endothelioma and a carcinoma, and another type of tumor which is not explainable.

Dr MacNeal: In the brain substance we have not demonstrated this endothelioma The only place we have been able to find it is in this one mass which was attached to the optic nerve and was growing freely in the sub-arachnoid space.

THE EXPERIMENTAL PRODUCTION OF SARCOMA OF THE LIVER OF RATS[1]

F. D. BULLOCK, M.D., AND M. R. CURTIS, PH.D.

(From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director)

The relationship between chronic irritation and the appearance of neoplasms in man has long been recognized. The best known examples are the tumors following soot or tar irritation, the Bilharzia, kangri, and betel nut cancers, and the new growths observed in x-ray and anilin workers. While the early literature of experimental cancer contains accounts of successful results in arousing malignant transformation of tissues by various forms of irritation, most of these reports are unconvincing owing to doubtful histological proof and inadequate biological data, and the exact nature of the growths obtained remains obscure.

In recent years interest in this subject was revived by the experiments of Fischer,[1] who by the injection of Scharlach R. elicited lesions in the skin of rabbits histologically resembling cancer. These lesions and similar ones produced by other observers, however, never metastasized nor were transplantable and they disappeared as the irritating material was absorbed.

Clunet[2] was able to obtain one neoplasm in a rat after producing x-ray burns in a large number of animals. This tumor, a sarcoma, was transplanted and yielded one temporary growth which later disappeared completely. By the same method Marie, Clunet, and Raulot-La Pointe,[3] produced a transplantable rat sarcoma. These experiments have been repeated on a large scale in the Crocker Laboratory on rats and rabbits but without the appearance of any tumors. Fibiger[4] in 1914 published detailed reports of nineteen rats in which hyperplasias of the gastric mucosa resembling carcinomata resulted from feeding the animals with cockroaches infested with the nematode worm, *Spiroptera*.

---

[1] The authors published "A Preliminary Report on the Experimental Production of Sarcoma of the Liver of Rats," in *Proc. Soc. Exper. Biol. and Med.*, 1920, xviii, 29–30.

His subsequent investigations[5, 6] increased the number of such hyperplasias to 84. In one group of rats of a particular inbred strain he obtained 54 tumors in the 134 animals which lived for 30 days or longer. In 8 of the 84 cases he observed lung metastases, thus proving that the tumors were biologically as well as morphologically, carcinoma. This investigator states: "*Spiroptera* cancer very exceptionally attains the stage of development distinguishable by macroscopic examination." He was unable to transplant these rat tumors, although he has recently reported[7] a propagable spiroptera carcinoma of the mouse stomach which he has carried through four generations of mice. By employing the same agent and method Fibiger[8] has produced

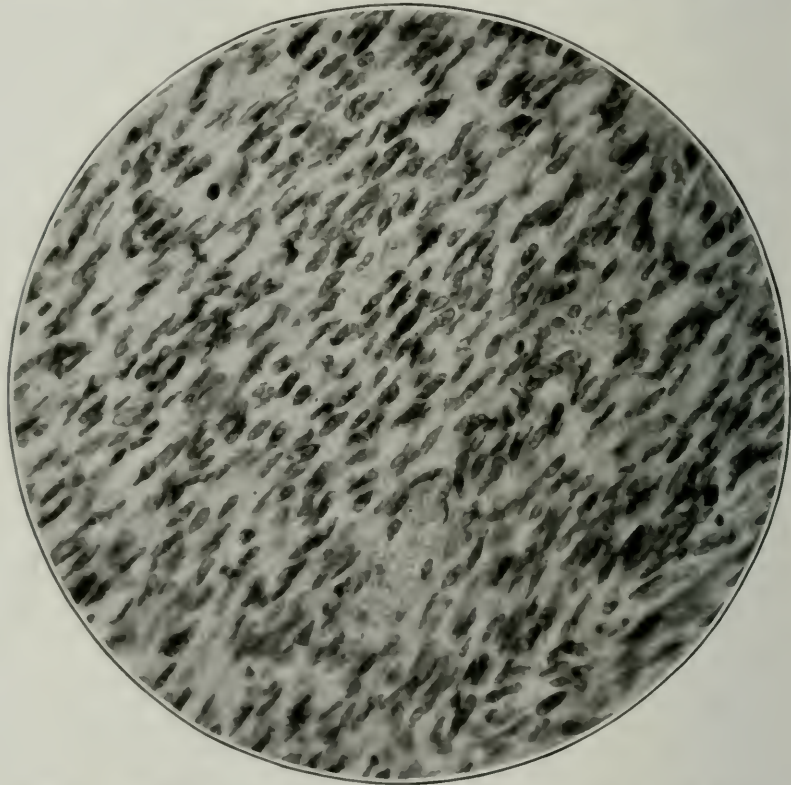


FIG. 1. Early spindle-cell tumor, IRS 8/0, shown in Fig. 5. × 400.

five epitheliomata of the tongue of rats, two of which showed metastatic deposits in the perineural lymph-spaces. Yamagiwa and Ichikawa[9, 10] have announced the successful production of epithelioma of the ear of rabbits by painting the inner surface of the ear repeatedly with coal-tar. They report twelve cases of carcinoma, but without giving the total number of rabbits treated. Of these twelve tumors three showed lymph-node metastases. However, these authors did not succeed in their attempts to transplant the tumors. The experiments of Yamagiwa and Ichikawa were repeated on mice by Tsutsui[11] and more recently by Fibiger and Bang.[12] These investigators repeatedly painted the skin of the body of the mice with coal-tar. Of the 67 mice em-

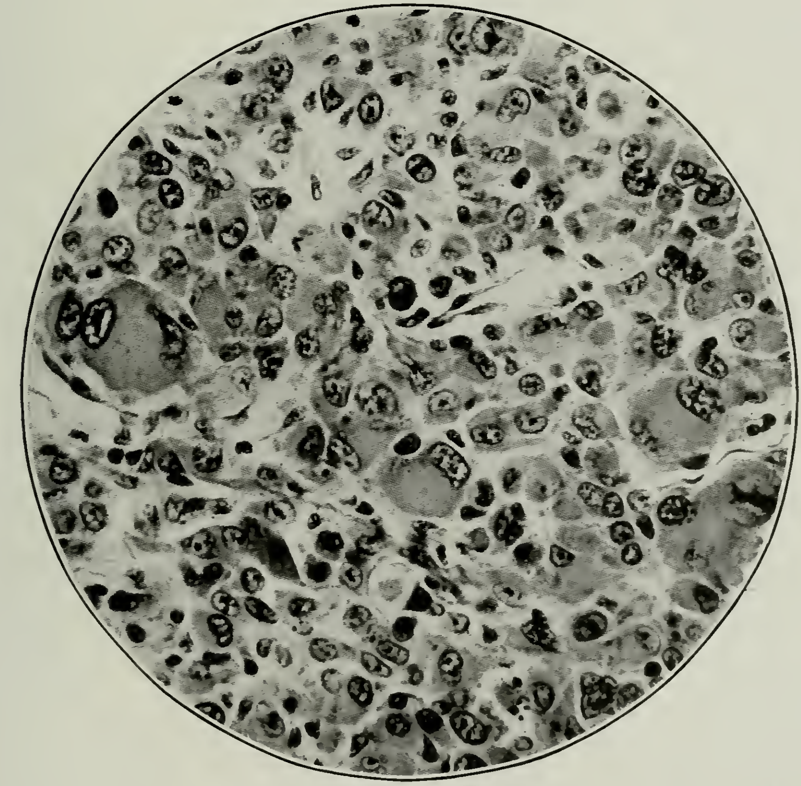


FIG. 2. Early polymorphous-cell tumor, IRS 9/0, shown in Fig. 4. × 400.

ployed by Tsutsui which lived over 100 days, 16 developed carcinoma, and in two cases metastases were found in the lungs. Fibiger and Bang reported the development of 22 carcinomata and two carcinosarcomata in 26 mice which lived six months or longer. Of these tumors, 6 metastasized in the axillary lymph-nodes and 2 in the lungs, and 3 grew on transplantation.

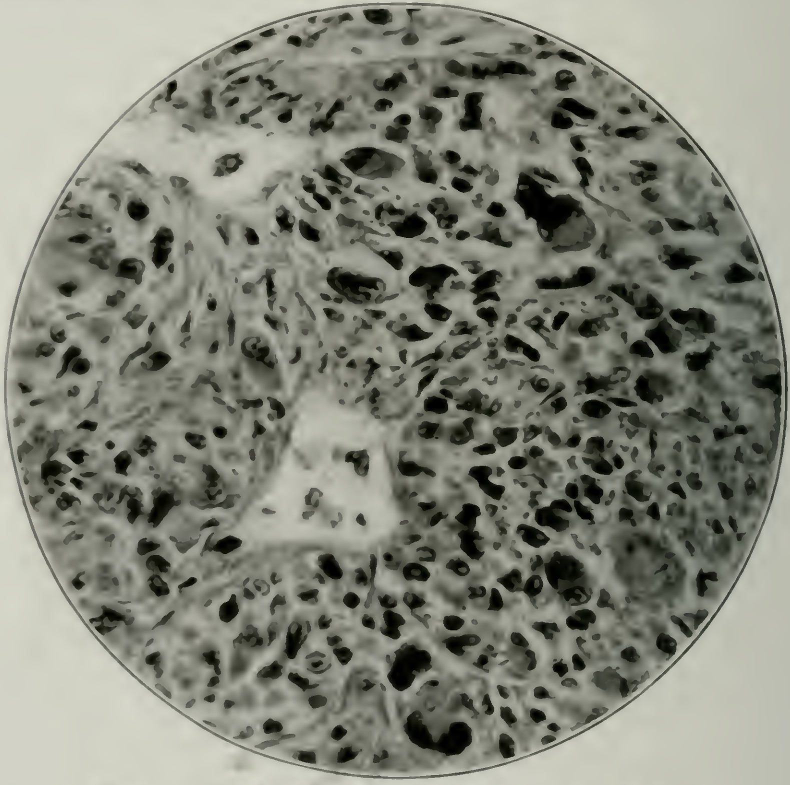


Fig. 3. IRS 3 0, showing the mixed-cell type. × 400.

Thus, so far a great amount of labor and a large number of animals have been required to produce a few tumors, most of which are not transplantable.

In previous papers from the Crocker Fund, Rohdenburg and Bullock[13, 14, 15] reported twelve spontaneous sarcomata of the liver of rats arising in the walls of cysts of *Cysticercus fasciolaris*.

and described six of these growths in detail. Since the last publication eight additional spontaneous rat sarcomata of similar origin have been observed, making a total of 20 cases. Only two of these tumors were transplanted.[15] One of these is now in the forty-sixth generation, the other was carried for over eleven months (14 generations), and then discarded. In the last of the publications referred to above, it was shown that of the thirty

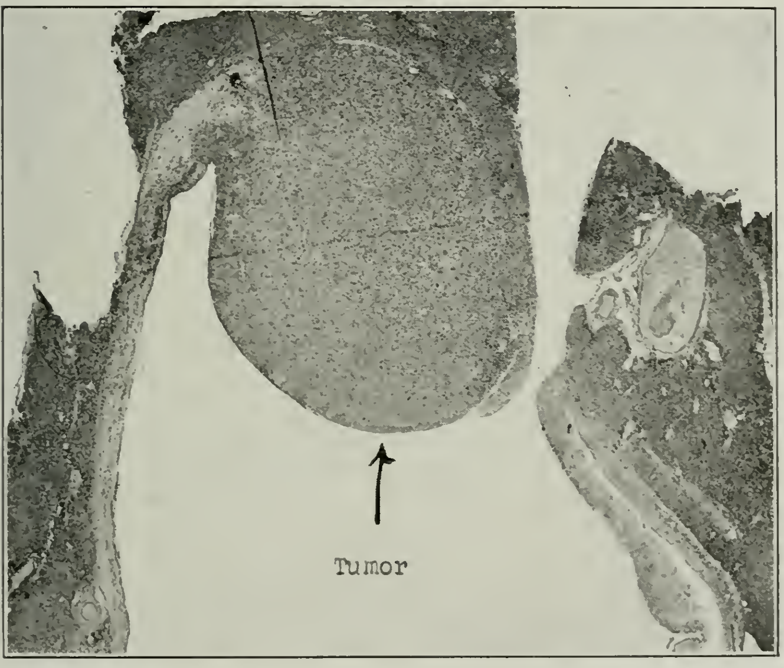


Fig. 4. Low power of an early intracystic polymorphous-cell sarcoma. IRS 9/0.

liver sarcomata of rats reported by other investigators, 90 per cent. were associated with the *Cysticercus fasciolaris*. Hirschfeld[16] recently reported an additional case of angiosarcoma of the rat liver associated with this parasite and in concluding his article stated that feeding experiments are in progress having as their object the production of sarcoma. However, he left to the imagination of the reader the kind of material with which he fed his animals, though the most probable inference from the context is that he employed the larvæ.

Infestation of the rat by *Cysticercus fasciolaris*, which is the larval stage of *Tenia crassicollis* of the cat, follows the ingestion by the rat of food contaminated with cat feces containing the eggs of this tapeworm. The outer membrane of the egg is digested away; and the onchosphere thus liberated penetrates a blood-vessel of the intestinal wall, and passes into the portal circulation, coming to rest in a capillary of the liver, where it begins its larval development. During the course of the second day

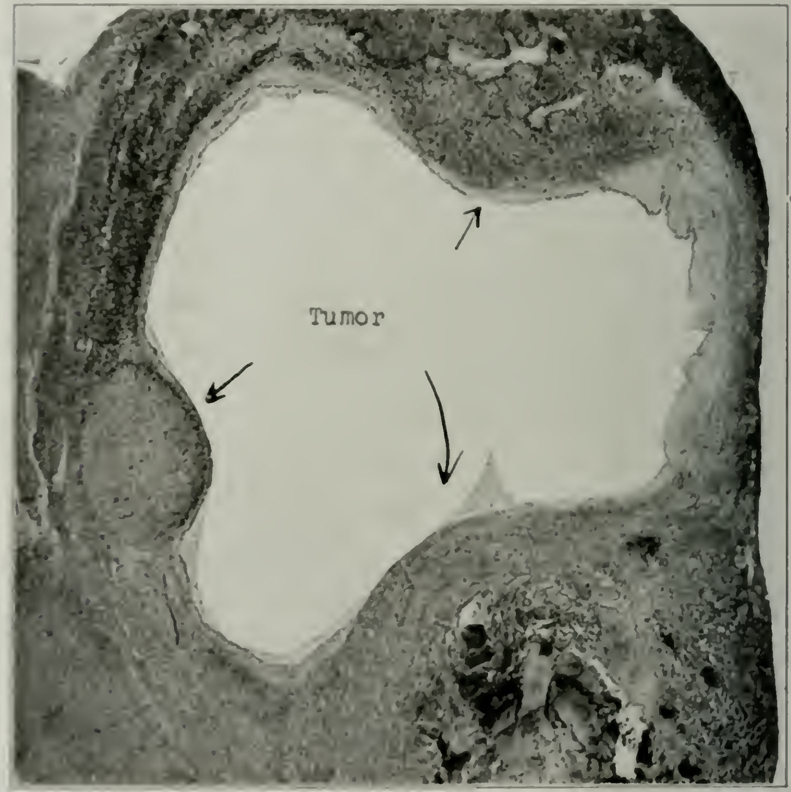


FIG. 5. Low power of IRS 8/0, showing nodules of spindle-cell sarcoma projecting into the cyst cavity.

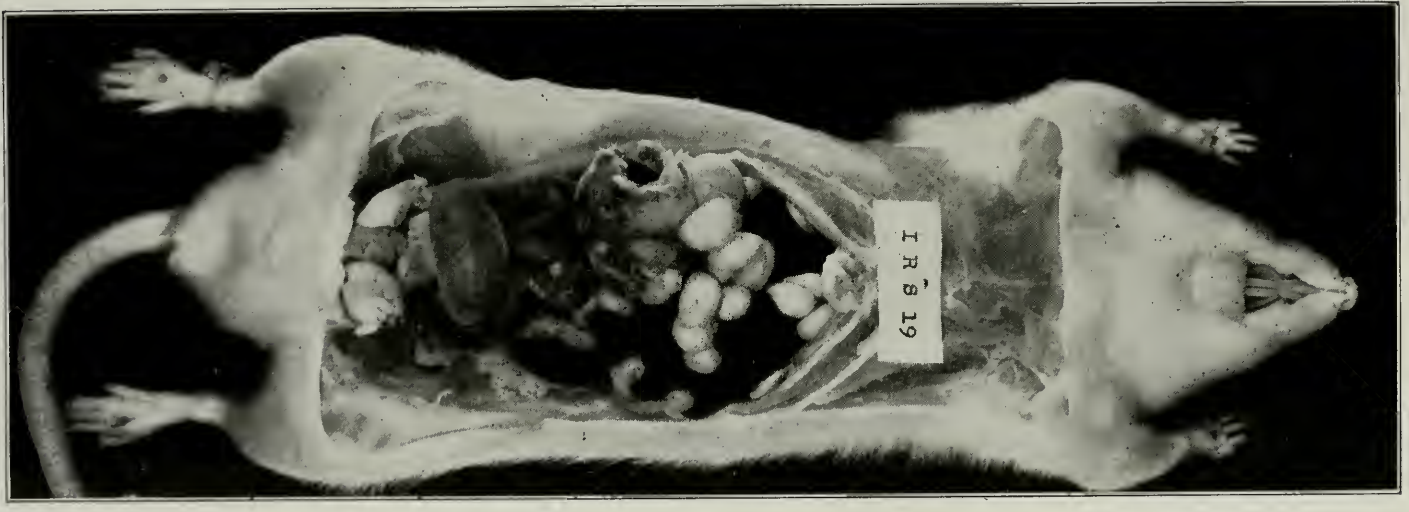


Fig. 6. IRS 19/0, from which a slice has been removed to expose the cyst cavity.

after feeding mice the eggs of this Tenia, Braun[17] found the larvae in the capillaries of the liver. After a series of reactions[1] in the tissues of the host which immediately surround the larva, there is gradually evolved a cyst wall of varying cellularity which encloses the parasite. Within the cyst the larva develops into a long, flattened segmented worm resembling an adult tape-

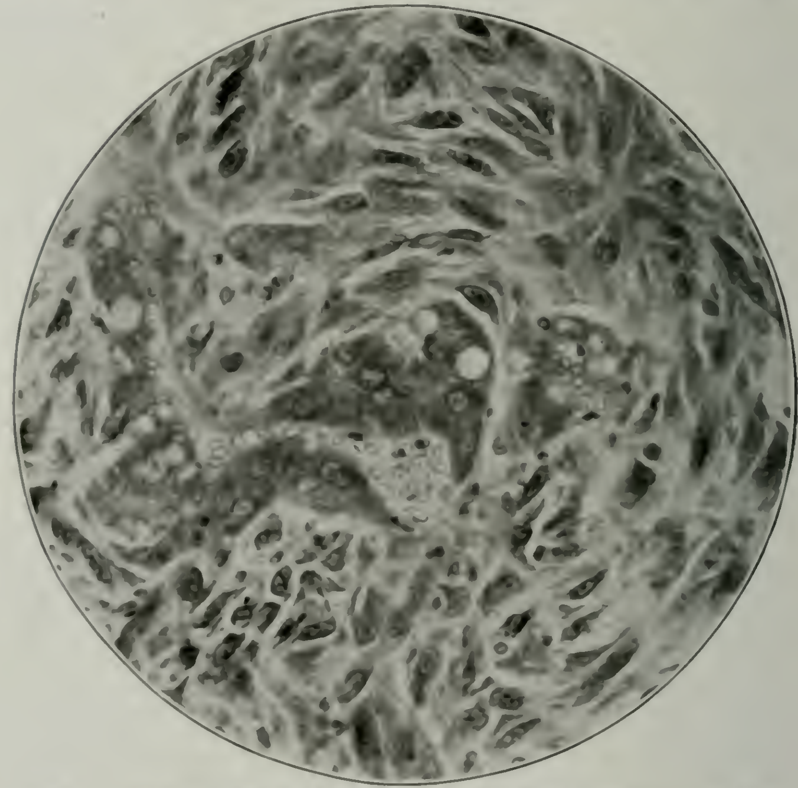


Fig. 7. IRS 1610, showing infiltration of the liver by the tumor. × 400.

worm, but without sexual differentiation. It lies free in the cyst cavity, bathed in a variable amount of thin, clear, straw-colored fluid. In many cases, through some influence of the worm, as yet undetermined, the cells of the cyst wall undergo active proliferation or even assume malignant properties.

[1] The histogenesis of the cyst will be considered in a subsequent report.

In March, 1917, Bullock and Rohdenburg attempted to induce sarcoma of the rat liver by employing *Cysticercus fasciolaris* as an agent. In that experiment 100 rats were fed with cat feces containing the eggs of *Tenia crassicollis*. Unfortunately, these rats early succumbed to rat typhoid then epidemic in the labora-

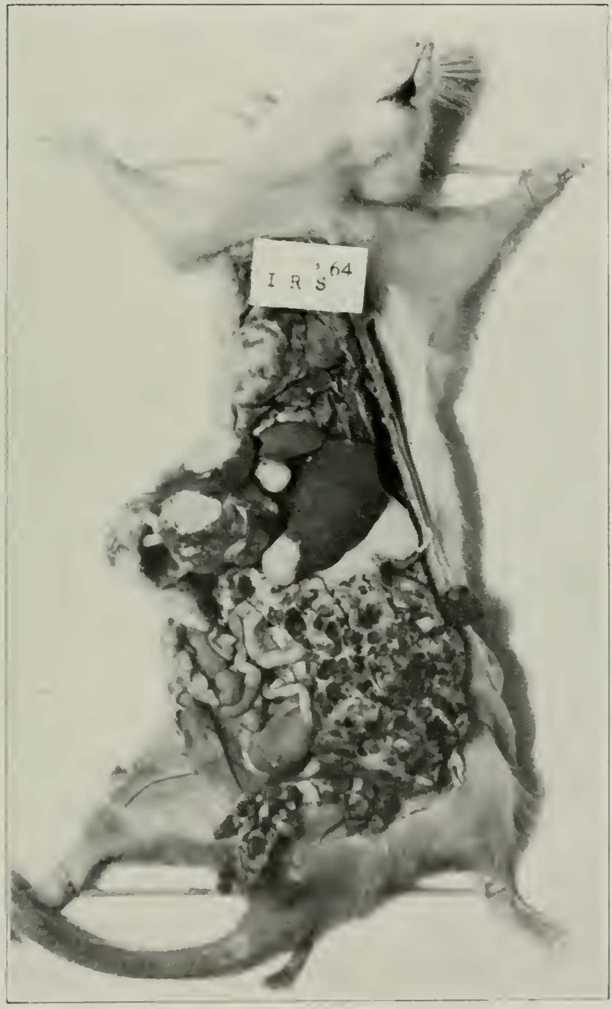


Fig. 8. IRS 64/0, showing primary tumor and general peritoneal metastases. The cyst had been opened to expose the cavity and parasite.

tory, and the experiment was not resumed until the fall of 1919 when it was undertaken on a larger scale by the present authors.

In October, 1919, 1,165 rats of five different strains and of estimated ages varying from 2 to 9 months were fed with Tenia eggs from cat feces. The feces were obtained in a fresh state from a single cat. This material was mixed thoroughly with water, and squeezed through cheese-cloth, and the expressed fluid either was allowed to settle or was centrifuged. The sediment was mixed with water sufficient to reduce the number of eggs per drop to about 10 to 30. The rats were fed *per os* with a medicine dropper, each animal receiving one or two drops (about 10 to 60 eggs). Preceding the feeding of each rat, the suspension of eggs was actively agitated before it was drawn up into the dropper in order to approach uniformity in the number of eggs administered.

To determine whether or not the animals were infested with the parasite a few rats from each group were killed and examined at varying intervals. In all these animals the larvæ had reached the liver; but in one group, composed of a particular strain of animals several months older than the others, the larvæ failed to grow. Consequently the animals of this group, comprising 600 originally, were killed and autopsied five months after they were fed. The small percentage of animals showing growing larvæ demonstrated the economic wisdom of this sacrifice. Of the remaining animals 279 were alive July 29, 1920, the day before the first tumor was found. By January 18, 1921, 230 of these had either come to autopsy by death from natural causes or been killed for confirmation of a clinical diagnosis of tumor. Fifty-five of these bore tumors which were recognizable in the gross; that is, 29 per cent. of the dead animals which were infested with the parasite, or 20 per cent. of all the animals alive when the first tumor was found, have shown tumors. Forty-nine of the 279 are still under observation. About 2,500 descendants of the original animals have been added to the experiment. They represent four generations and are all of known ages; and a high percentage is fully pedigreed. Thirty of the first generation of these descendants have thus far developed tumors. These with the fifty-five from the original stock make a total to date of 85 tumor-bearers.

These tumors belong to two histological types or to a mixture of these, being composed of either spindle or polymorphous cells, or containing both kinds in varying proportions (Figs. 1, 2, and 3).

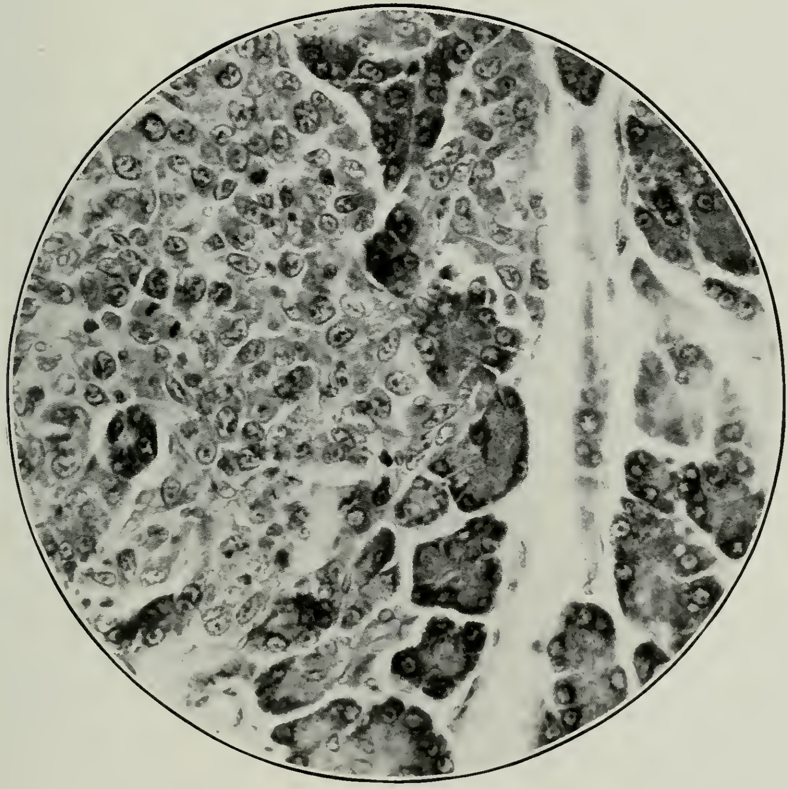


FIG. 9. Omental metastases of a polymorphous-cell sarcoma, IRS 4/0, invading pancreas. × 400.

Various stages of growth of these sarcomata are represented in the above series. The smaller tumors generally occurred as single or multiple localized nodules in the cyst wall which either encroached upon the cyst cavity or projected externally. They involved either the inner or the outer zone of the cyst wall or its entire thickness. Other small tumors appeared as diffuse thickenings of the cyst wall, which included a part or the entire area of

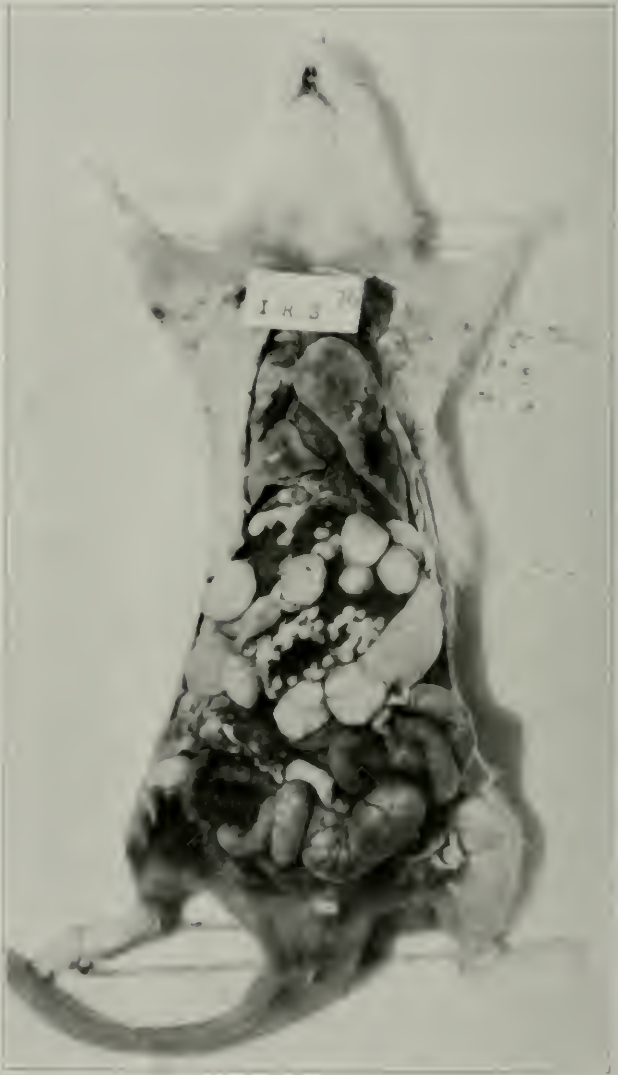


Fig. 10. IRS 76/0, showing relatively small tumor and discrete and confluent secondary deposits on the surface of the liver.

the cyst. Fig. 4 is a low power photomicrograph of a portion of a cyst wall containing the early polymorphous-cell tumor shown in Fig. 2. A cyst wall with nodules of pure spindle-cell sarcoma projecting into the cyst cavity is shown in Fig. 5. The high power appearance of one of these nodules is shown in Fig. 1.

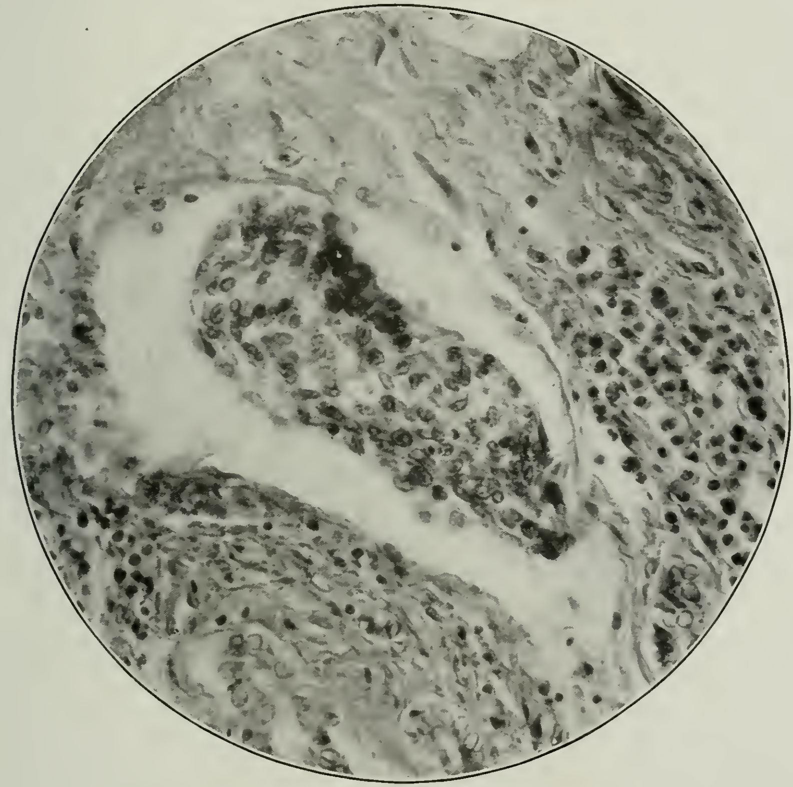


FIG. 11. Embolus of a spindle-cell sarcoma, IRS 1/0, occupying a blood-vessel in the wall of a cyst. × 400.

The site or sites of origin of the tumor in the cyst wall and the direction and rate of tumor growth probably explain the position of the cyst in the larger tumors. It was either buried in the tumor substance, being centrally or eccentrically placed, or it was situated on the surface of the tumor, the free wall being generally completely transformed into sarcoma. Fig. 6 shows a photograph of a rat with a moderate sized tumor from which a slice has been removed in order to expose the cyst cavity. Sometimes, as in this case, the cavity remained large; but at other times it was partly or almost completely obliterated by the ingrowth of the surrounding tumor. Gross examination was sufficient to disclose the presence of a parasite in all but fourteen of the tumors.

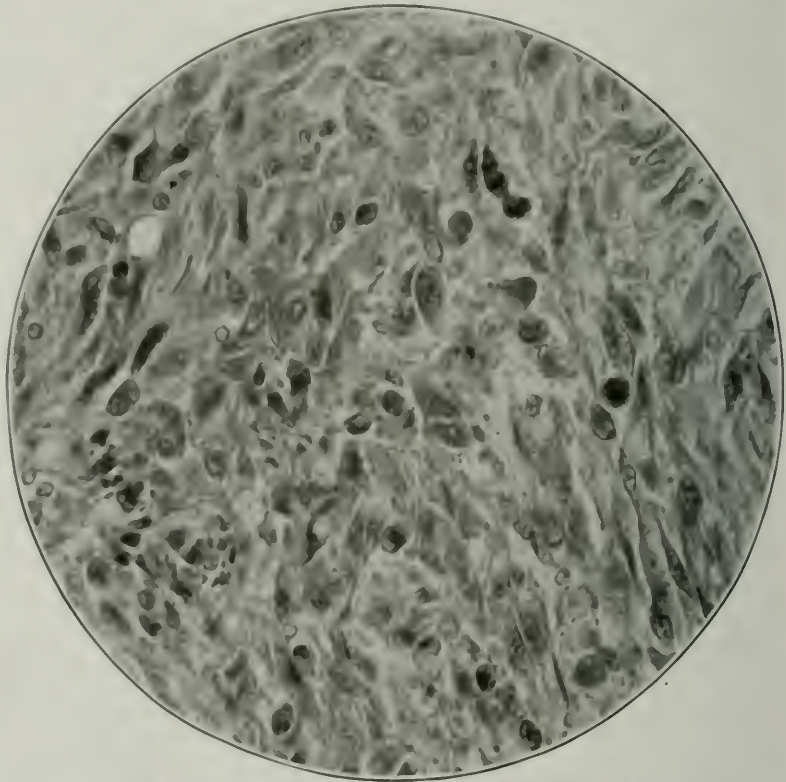


FIG. 12. Tumor from the first transplantation of IRS 3/0. × 400.

In seven of these cases there were cyst-like cavities in the tumors and free worms in the peritoneal cavities. Each of the other seven showed extensive necrosis, which may have destroyed and effaced both cyst and parasite. However, there is a possibility that the latter seven tumors originated in the liver outside the walls of the cysts, although early extracystic tumors have not been observed. Besides the primary tumor cyst other cysts in the neighborhood were frequently involved by the extension of the growth. On the other hand, in a few instances two cysts were so placed in one tumor mass that the most probable inference was that they represented independent tumor foci, which later coalesced.

These induced sarcomata often grew very rapidly as was evidenced by a two or three fold increase in size in the course of a week or ten days, the tumor size being estimated by palpation. They sometimes replaced a large part of the liver substance and attained a size several times as great as that of the normal organ. Fig. 7 shows a photomicrograph of one of these tumors invading the surrounding liver. The neoplasms occurred in all parts of the liver, the percentage of tumors in any one lobe corresponding roughly to the proportionate size of the lobe. In the gross the tumors were either smooth or nodular, and often showed necrosis, associated with hemorrhage. They varied in consistency from firm and elastic to soft and brainlike, and were generally richly supplied with blood vessels.

Gross metastases were almost always associated with the larger tumors, and frequently occurred with tumors of intermediate sizes. In 52 of the 85 cases metastases were distinguishable in the gross. The smallest tumor in the series which showed macroscopic metastases measured 1.5 x 1.3 x 1 cm. The omental tissues were the most frequent site of secondary tumor deposits, and were often plastered to the surface of the tumor. Where metastasis was generalized, there was involvement of the omentum, the mesentery, the serous surfaces of the viscera, the diaphragm, and the abdominal wall.

Fig. 8 is a photograph of a specimen showing rather generalized metastases in the peritoneum. The secondary tumors sometimes infiltrated the organs upon which they rested (Fig. 9). Such metastatic tumors were frequent on the surface of the liver (Fig. 10), and were often found on the walls of other cysts. Not infrequently they invaded the muscles of the abdominal wall and diaphragm; and in a few cases, where the diaphragm was penetrated by the growth, tumor nodules were observed on the pleura and pericardium, and in one instance there was invasion of the heart and lungs. These secondary tumors are probably often the result of implantation of tumor cells, but some are undoubtedly true metastases since tumor emboli have been demonstrated in the blood vessels. A sarcoma embolus is shown in Fig. 11.

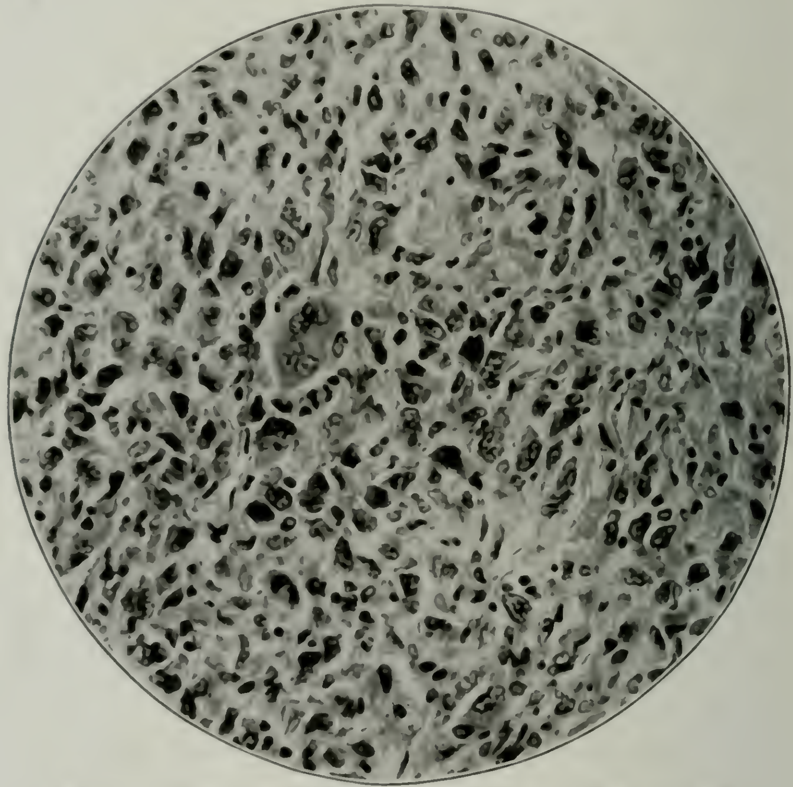


Fig. 13. Tumor of the first transplantation of IRS 4/0. × 400.

Most of these induced tumors which were transplanted into the subcutaneous tissues of rats showed a moderate to a high percentage of successful inoculations and many of the daughter tumors grew progressively and rapidly and maintained the morphological type of the original tumor. Figs. 12 and 13 show the histological appearance of tumors of the first transplantation of IRS3 and IRS4, and should be compared with Figs. 3 and 9 respectively; and Figs. 16 and 17 should be compared with Fig. 15. Of the 43 thus tested only two failed to grow and two others were lost in the second generation. This high percentage of transplantability contrasts markedly with the few transplantable growths obtained by other methods and proves the malignant

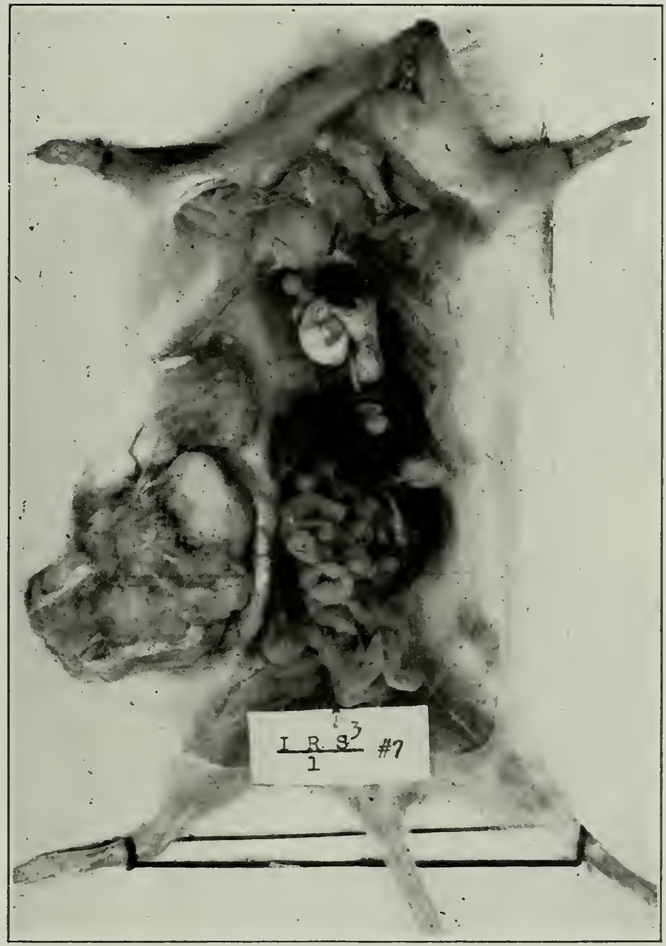


FIG. 14. Transplanted tumor, IRS 3/1A, No. 7, showing metastases in the neck and lungs.

nature of these sarcomata. Some of the transplanted tumors of certain strains showed a tendency to recede after growing progressively for varying periods of time; others continued to grow progressively and ultimately caused the death of the rats. Some of them reached enormous sizes, and in several cases the tumors weighed more than their hosts. The first generation of transplants from each of 20 different induced sarcomata has been observed for a sufficiently long period to distinguish between progressively growing and receding tumors. The inoculation results varied from a single progressively growing tumor and twenty-five negative (IRS 7/1A), to twenty progressively growing and seven receding tumors (IRS 38/1A). In all twenty series 768 animals were

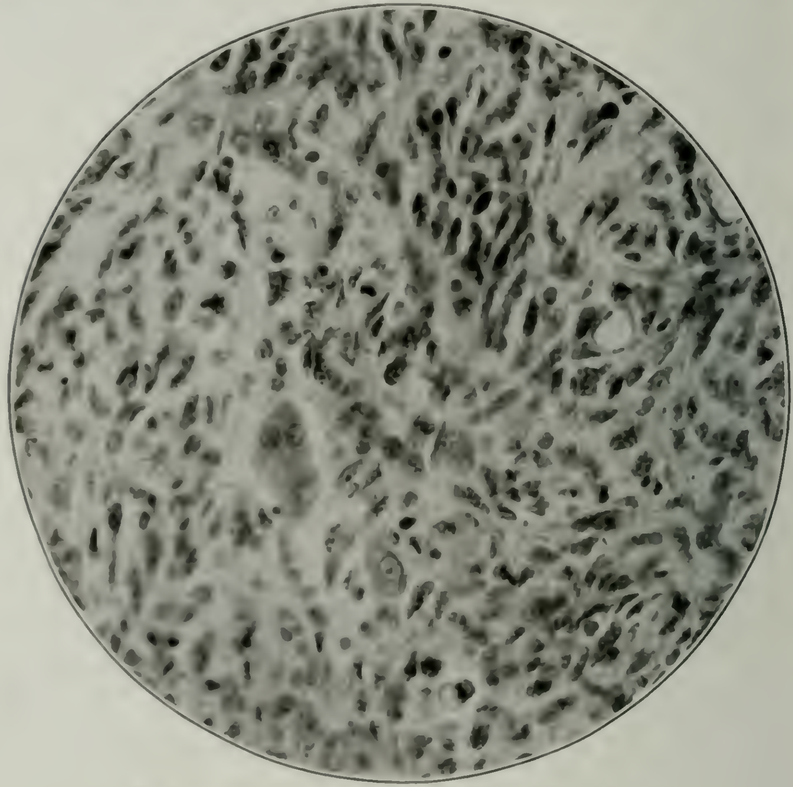


Fig. 15. Spindle-cell sarcoma, IRS 38/0. × 400.

inoculated. Of these 363 were negative, 216 had receding tumors, and 189 had progressively growing tumors. That is, on an average the transplantation of one of these induced sarcoma resulted in 24.6 per cent. progressively growing tumors, 28.1 per cent. receding tumors, and 47.3 per cent. negatives. These percentages of successful inoculations are high compared with those usually obtained from the transplantation of spontaneous rat and mouse carcinomata. The recession of some of the tumors is quite characteristic of rat sarcomata in general. Lung metastases of the transplanted tumors of three different tumor strains have thus far been observed. One of these showed also a large secondary growth in the neck (Fig. 14). Photomicrographs of the primary

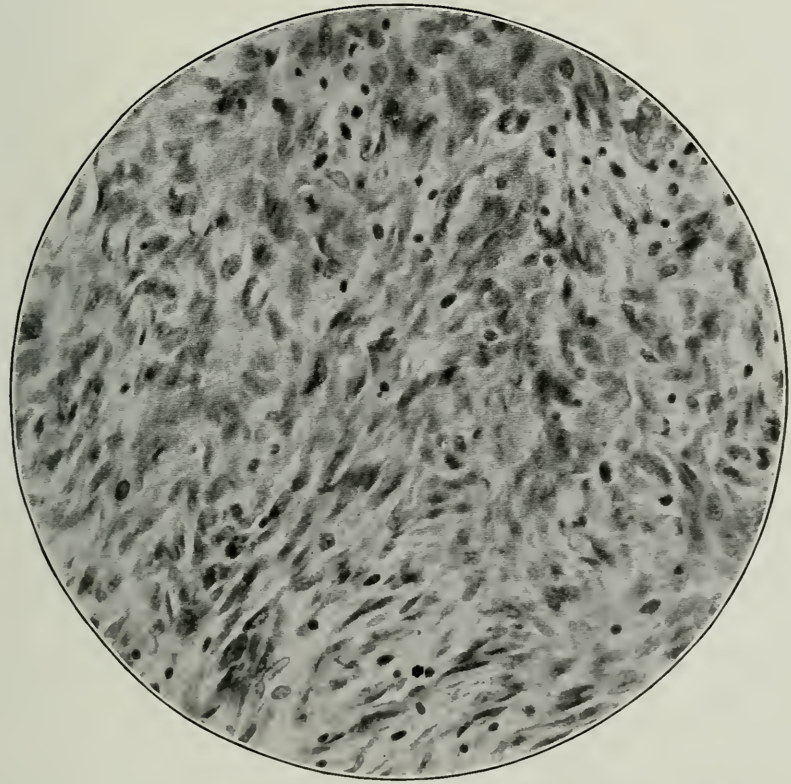


FIG. 16. Tumor from the first transplantation of IRS 38/0. × 400.

tumors, the transplanted tumor, and a lung metastasis of one of these strains are shown in Figs. 15, 16, and 17.

Some of the transplanted tumor strains were discarded after a few generations; others are still under observation and the first two which were transplanted are now in the sixth and fifth generation, respectively.

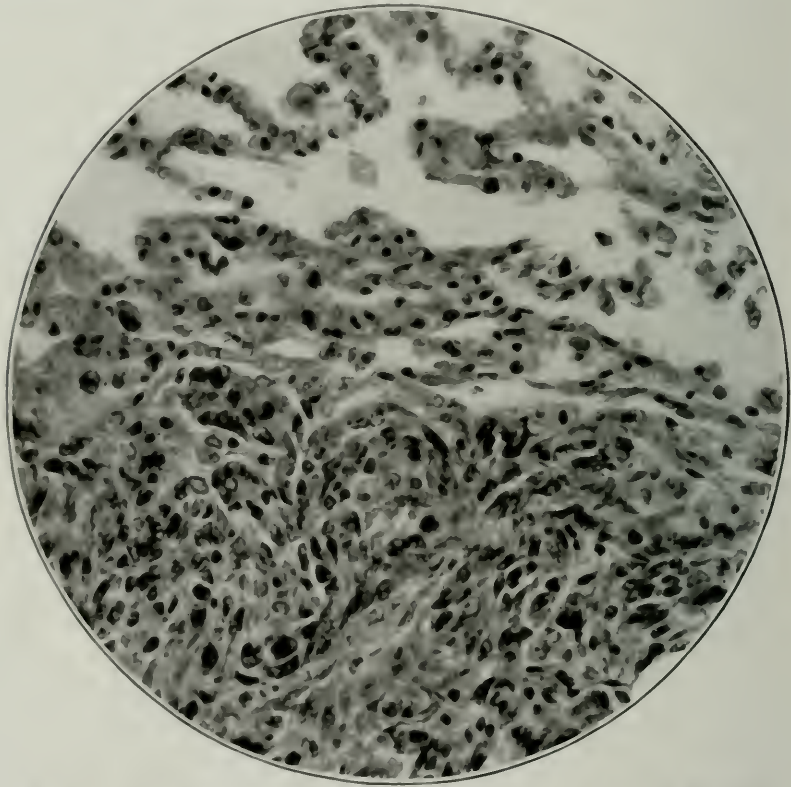


Fig. 17. Lung metastasis of the transplanted tumor shown in Fig. 16. × 400.

All the tumor-bearing rats presented multiple cysts in the liver varying from 6 to 84 in number. In a high percentage of these animals only one of the cysts was primarily involved in the malignant process. In a few instances, however, two to four cysts, situated either close together or widely separated and in different lobes of the liver, showed tumors of approximately the same size. In these cases metastases were not generalized and it seems probable that the tumors were of independent origin.

The tumor cysts contained larvæ the condition of which apparently depended upon the state of preservation of the cyst wall. When the cyst wall was partly uninvolved by the tumor, or consisted largely of healthy tumor tissue, the parasite was alive and intact, and measured from 15 to 38 cm. in length. These larvæ resembled the larvæ of the healthy uninvolved cysts. Where the transformed cyst wall was involved in the tumor necrosis the larva was usually dead, and distorted, and often necrotic and fragmented. It seems probable, therefore, that the live worm initiates the malignant process, and that the death of the worm is secondary to the growth and necrosis of the tumor.

The duration of the irritation necessary for the production of these tumors evidently varies within wide limits. A small but definite sarcoma was discovered as early as 248 days after the animal was fed cat feces. Recently, however, another rat has shown an early tumor 466 days after the ingestion of cat feces, and it is very probable that tumors will continue to appear in the 49 rats of the original group which are still under observation.

The tumor-bearing rats varied in age from 9½ to 18 months. Like a majority of the non-tumor-bearing animals which have come to autopsy, most of them were well nourished but showed no great excess of adipose tissue. On the other hand, tumors occasionally occurred in emaciated or in fat animals. Rats of both sexes and from each of the five strains tested were represented in the tumor series. Inspection of the data suggests that there is an age and probably also a strain difference in the susceptibility to infestation by the parasite, since young animals and certain strains seem to be most susceptible. Possibly there is also a strain difference in predisposition to the neoplastic conversion of the cyst. These and other similar problems can not be intelligently discussed until the rapidly accumulating data are analyzed.

Besides the 85 macroscopic tumors considered in the paper the histological material includes various stages in the malignant transformation of the cyst wall and presents an unusual opportunity for the study of the histogenesis of these sarcomata.

Summary

1. Spindle and polymorphous-cell sarcomata have been induced in the livers of 85 rats through the mediation of the *Cysticercus fasciolaris*, the larval stage of the *Tenia crassicollis* of the cat.

2. Young rats of certain strains seemed to be most susceptible to the parasite.

3. Most of the tumors undoubtedly originated in the walls of parasitic cysts, and the others were probably of similar origin.

4. The duration of the irritation necessary for the production of tumors is evidently very variable, since one tumor was observed eight months after the animal had ingested the eggs, and a small tumor was lately found in an animal fifteen months after feeding.

5. The series represented all stages of tumor development from small single or multiple localized tumor nodules, or diffuse neoplastic areas in the cyst wall, to tumors which replace a large part of the liver and are several times the size of the normal organ.

6. The malignant nature of these tumors is evidenced by invasive growth, metastasis formation, and transplantability into other rats.

7. The invasive power is shown, not only by the primary induced tumors which early infiltrate the adjacent liver, but also by the metastatic tumors which often invade the organs upon which they rest.

8. The high percentage of transplantable tumors (90 per cent. of the 43 tested) is in sharp contrast with the few transplantable growths reported by other investigators.

9. The larvæ in the tumor cysts were usually alive and showed no apparent difference from the larvæ of other cysts not surrounded by tumor material. Dead larvæ were found in the tumor cysts only when tumor necrosis involved the cyst wall.

10. The tumor bearing rats were 9½ to 18 months of age. They were of both sexes and of five strains.

11. This simple and practical method of inducing a high percentage yield of sarcomata in animals suitable for experimentation may be of service in several lines of cancer research including (1) the histogenesis and diagnosis of sarcoma, (2) the genetic behavior of immunity and predisposition factors, (3) prophylaxis, and (4) tumor therapy.

ADDENDA

From January 18, 1921, when this report was made, to May 7, 1921, cysticercus tumors developed in 125 additional rats in this experiment, making a total of 210 animals in which sarcomata have been experimentally produced.

References

1. FISCHER: *Verhandl. d. deutsch. path. Gesellsch.*, 1906, x, 20.
2. CLUNET: Recherches expérimentales sur les tumeurs malignes, Paris, 1910, p. 297.
3. MARIE, CLUNET, AND RAULOT-LAPOINTE: Assoc. franc. p. l'étude du cancer, 1912, p. 239.
4. FIBIGER: *Ztschr. f. Krebsforsch.*, 1914, xiv, 295.
5. FIBIGER: *Det. Kgl. Danske Videnskabernes Selskab. Biologiske Meddelelser,* 1918, i, 9.
6. FIBIGER: *J. Cancer Research*, 1919, iv, 367.
7. FIBIGER: *Det. Kgl. Danske Videnskabernes Selskab. Biologiske Meddelelser,* 1919, i, 14.
8. FIBIGER: *Det. Kgl. Danske Videnskabernes Selskab. Biologiske Meddelelser,* 1918, i, 10.
9. YAMAGIWA AND ICHIKAWA: *Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo*, 1915–16, xv, 295–344: 1917, xvii, 19: 1918, xix, 483.
10. YAMAGIWA AND ICHIKAWA: *J. Cancer Research*, 1918, iii, 1.
11. TSUTSUI: Gann, 1918, xii, 17.
12. FIBIGER AND BANG: *Det. Kgl. Danske Videnskabernes Selskab. Biologiske Meddelelser,* 1921, III, 4.
13. BULLOCK AND ROHDENBURG: *J. Med. Research*, 1913, xxviii, 477.
14. BULLOCK AND ROHDENBURG: *J. Cancer Research*, 1917, ii, 39.
15. ROHDENBURG AND BULLOCK: *J. Cancer Research*, 1916, i, 87.
16. HIRSCHFELD: *Ztschr. f. Krebsforsch.*, 1917, xvi, 95.
17. BRAUN AND SEIFERT: Die tierischen Parasiten des Menschen, Wurzburg, 1915, 5th Edition, Teil I.

Discussion:

DR. EWING: This study is obviously of great interest and importance. It seems to me a parallel to Fibiger's results. The tumors seem to have the biological characteristics which we are accustomed to insist on for a malignant process to a greater extent than Fibiger's did, although I feel that Fibiger's processes in all essential respects were experimentally produced carcinoma. One matter that interests me particularly is the histogenesis of the tumor. I would like to know what Dr. Wood thinks of the exact cell origin. Is it a type of reaction which can be compared with granulation tissue; where does it originate, and what is its significance? I think it might throw some light on the nature of this process if one could compare in the rat the connective tissue reactions to other irritants which do not go on to sarcoma. It may be that the rat's fibroblasts or epithelial cells or blood vessels respond to certain standard irritants much more actively than human tissues do, and if that is the case, then the significance of this sarcoma in the rat, while it is true sarcoma for the rat, may not have so direct a bearing on the study of sarcoma in man. I can well conceive that in such an animal as the rat connective tissue proliferation is very much more readily incited than it is in man, and that such processes as we would be inclined to regard as hypertrophic exuberant granulation tissue in man are comparable in the rat to a process which we call sarcoma. That will not alter at all the fact that this tumor is malignant for the rat.

Another point of interest concerns the question of morphological diagnosis of malignant tumors in man. Dr. Wood says that Fibiger went a little too far in attributing to some of his early proliferative processes the full significance of malignant tumors. I think that Dr. Wood and his associates are perhaps erring in the other direction.

In regard to the interpretation of these suspicious malignant-looking processes in man, I think they should be estimated from the clinical standpoint. They believe that the epithelial proliferations produced by various irritants are not true cancers, because they disappear when the irritant is removed, and consequently that similar malignant looking histological processes in man should not be regarded as cancer. I have observed the disappearance of seborrheic dermatitis of the lip after it had assumed some of the clinical characteristics of cancer and when it had probably reached a stage comparable to some of these experimental cancers. But the great majority of such lesions in man go on to develop cancer and from the clinical standpoint it is wise to regard them as early cancer. From that point of view all these observations confirm me in feeling that we must consider carcinoma not as a fully developed disease, but as a process which takes time and passes through stages of evolution, and that it is possible to recognize these stages and to determine by experience about what they are going to do. I am not inclined to think that the observations on experimental tumors or tumor-like processes in rats are apt to dislodge us from the position we hold in diagnosing these suspicious processes in man, for I shall continue to recognize as pre-cancerous or as early cancer the same processes in the breast which I have found heretofore suggested malignancy, in spite of the fact that many of these experimental processes disappear if the irritant is removed.

I have formed the impression that Drs. Rohdenburg and Bullock are a little less positive than they were originally. I think I recall a statement at one time by these authors casting aside the significance of the partially developed keratoses and downgrowths of epithelium, but in their last report I think I recall that they admitted that they had seen some of them go on and develop further phases of a true carcinoma in the clinical sense, even with the production of metastases. Whether they do admit it or not, it seems likely that they are producing carcinoma, and if they keep on long enough, they will get metastases. Dr. Wood gets his very easily. All these things are extremely important. They make one think about the conditions which surround the beginnings of cancer.

Dr. Larkin: I am interested in Dr. Wood's presentation, and the histological pictures have convinced me as to the nature of the tumor. Several of the slides show general widespread metastatic involvement in the omentum, lung, and elsewhere, and prove that the growths are malignant.

Dr. Rohdenburg: I think I can answer one of Dr. Ewing's questions. Owing to our inability to obtain access to the foreign literature during the war, we were not cognizant of the fact that Fibiger had been able to transplant his tumors, consequently one of our criticisms had already been answered, and of course falls. We did not have the opportunity until very recently of seeing Fibiger's slides. If you take some of his and put them beside ours, without seeing the labels, I doubt whether you could tell which was which. We have tried various ways of irritation in the rat liver. We have used pith balls and various other forms of irritation of solid and semisolid characters, such as vaseline, and injected them directly into the liver. The connective tissue reaction was very different from that obtained in the wall of the cyst. Not all cysts, as Dr. Wood has said, become malignant. Those that do not become malignant are surrounded by hyaline connective tissue.

Dr. Ewing: Did you not conclude that your specimens which are identical with those of Fibiger are true carcinoma?

Dr. Rohdenburg: No, the lesions we were able to produce were not carcinomata; however, I believe that if we could keep up the irritation sufficiently long the lesions would become malignant. When you inject a solution of Scharlach R it is encapsulated by the epithelium, and it becomes impossible to duplicate mechanically what the cysticerci and the nematodes do naturally. I am willing to admit that if you could keep up the irritation it might become malignant. Our failure is not due to lack of patience as Ichikawa has insinuated,—it is due to the inability to reproduce the necessary mechanical conditions. Our irritation tumors have never formed metastases.

Dr. Ewing: May I ask the authors if they entertain any sympathy with Borrel's conception that in the case of those worms which produce malignant tumors there is a virus or a parasite in the worm which travels through to the cells which are invaded and thus produces a tumor as the direct result of the infection?

Dr. Rohdenburg: I do not. In the first place all the ova used in the experiments reported by Dr Wood came from one cat. The cat feces were ground up and emulsified, centrifuged, and standardized as to ova to one drop. The rat is held; the mouth is opened, and one drop put down the pharynx. It would be logical to conclude that if one ovum were infected in Borrel's sense then all that group would be; therefore all cysts should produce tumors; while the developing cysts are multiple, the tumors are usually single.

Dr. Jobling: Were the tumors observed sufficiently early to determine if the growth developed from one point of the surrounding capsule, or if it was more general in origin?

Dr. Wood: To answer Dr. Jobling's question first: we got the tumors at varying stages, because it is not always possible to make an early diagnosis. Some of the early tumors which were obtained showed a considerable tumor on one side and a little one on the other. There were a number of very small tumors which started from one point in the capsule.

As to Dr. Ewing's question on the histogenesis of the tumor tissue, we are not prepared to answer that. It comes from the connective tissue of the liver, but we have not had time enough to study details as yet.

I was interested in hearing Dr. Ewing say that there are pre-cancerous phases when a tumor goes through a stage when it is not a tumor. It cannot be recognized microscopically when it is not malignant, but gradually shifts over to something that does not behave quite right, and then the vital question arises whether the growth is pre-cancerous or cancerous. That is just the point I was trying to make; for example, I have a series of slides from a case of x-ray dermatitis in which half of the tumor has been sectioned, and a number of pathologists have made a diagnosis of epithelioma, but the other half of the tumor spontaneously disappeared. A thing that disappears spontaneously can hardly be put into the class of malignant tumors. It is hard to tell whether many of the very early tumors on the hands and lips are going to be malignant a month from now, or whether they are malignant at the moment. Anyone who has seen Dr. Rohdenburg's slides of irritation growths would make a diagnosis of carcinoma morphologically. If you see gastric tubules extending down to the serosa of the stomach you are apt to make a diagnosis of carcinoma, but when after removal of the source of irritation from the rat's stomach the tumor disappears, it can hardly be called malignant. It is well to remember that the pathologist originally knew nothing about malignancy until the surgeon told him that a certain type of tumor recurred. That is the basis for malignancy. Anyone who looks at a cellular cystadenoma of the breast would assume that it was malignant from the morphology, but I have a collection of forty or fifty specimens which the average beginner would call malignant, and yet the tumor has never returned. In some of these the tumor was only partially excised, but there has been no recurrence. We must therefore believe that such suspicious tumors are clinically benign. I still stick to my point, and I believe that Dr. Ewing agrees with me, that there are tumors which from the purely morphological point of view it is not always possible to designate as benign and malignant. The fibrosarcomata of the skin are a good example. As to these experimental tumors, and the question whether they are granulation tissue: they are not. They are definitely sarcoma. When there are metastases all over an animal the tissue is certainly not granulation tissue. When such tumors can be inoculated through five generations they are not composed of granulation tissue. I agree that a sarcoma in the rat is not a sarcoma in the human being. It is simply a peculiar type of tumor, and it is well known that rats are apt to have sarcomata and mice carcinomata. In dogs the tumors of the breast are carcinomata or sarcomata, and are not continuously transplantable. These are biological features showing how each animal has its own peculiar tumors.

VOLUME XX, 1920

INDEX

A

Acute yellow atrophy, a case of, with compensatory changes in the liver. E. Moschcowitz .. 54
Aneurysm of the hepatic and gastro-duodenal arteries, with rupture of the aneurysm into the duodenum. Henry R. Muller 46
Avitaminoses, the, and vitamines. Casimir Funk 119

B

Besredka's method of oral immunization of rabbits with ox-bile and para-typhoid vaccine. Abraham Zingher and David Soletsky 133
Bishop, Louis Faugeres. Localized changes in the heart muscle as determined to be in the right bundle branch by the electrocardiograph 70
Bronchus, carcinoma of the, with thrombosis of the superior vena cava. Ralph G. Stillman 66
Brown, Wade H. Experimental syphilis 96
Bullock, F. D., and Curtis, M. R. The experimental production of sarcoma of the liver of rats 149

C

Carcinoma of the bronchus with thrombosis of the superior vena cava. Ralph G. Stillman 66
Carcinoma, metastasis of, into an endothelioma of the optic sheath. Martin Cohen and Ward J. MacNeal 145
Carcinoma, quiescent metastatic gastric. G. L. Rohdenburg . 141
Cecil, Russell L. The pathology of experimental pneumonia 62
Cohen, Martin, and MacNeal, Ward J. Metastasis of carcinoma into an endothelioma of the optic sheath 145
Colloidal gold solution, a simpler way of preparing. Max Lederer 87
Curtis, M. R., and Bullock, F. D. The experimental production of sarcoma of the liver of rats 149

D

Dieterich, Frederich H. A case of right-sided endocarditis (*Streptococcus viridans*).. 5

E

Eggstein, Andrew E., and Frosch, Herman. A case of gastroileostomy surviving operation five years 9
Electrocardiograph, localized changes in the heart muscle as determined to be in the right bundle branch by the. Louis Faugeres Bishop .. 70

Encephalitis lethargica, experimental studies in. Leo Loewe and Israel Strauss 18

Endocarditis (*Streptococcus viridans*) a case of right sided. Frederich H. Dieterich 5

Endothelioma of the optic sheath, metastasis of carcinoma into an. Martin Cohen and Ward J. MacNeal 145

Experimental syphilis. Wade H. Brown 99

F

Frosch, Herman L., and Eggstein, Andrew E. A case of gastroileostomy surviving operation five years 9

Funk, Casimir. Vitamines and the Avitaminoses 119

G

Gastric carcinoma, quiescent, metastatic. G. L. Rohdenburg 141

Gastroileostomy, a case of, surviving operation five years. Andrew E. Eggstein and Herman L. Frosch 9

Glycemic reaction, its clinical significance, and its relation to immunity. G. L. Rohdenburg 1

H

Heart muscle, localized changes in, as determined to be in the right bundle branch by the electro-cardiograph. Louis Faugeres Bishop 70

I

Immunity, the glycemic reaction, its clinical significance and its relation to. G. L. Rohdenburg 1

Immunization, oral, of rabbits, with ox-bile and paratyphoid vaccine, Besredka's method of. Abraham Zingher and David Soletsky 133

Influenza epidemic of January-February, 1920, pathological findings in 17 cases of pneumonia, during the. Henry E. Meleney and Alwin M. Pappenheimer 56

L

Lederer, Max. A simpler way of preparing colloidal gold solution 87

Leucopoiesis and spermatogenesis, the relation between, in acute infection. Henry E. Meleney and Harold Linsky 117

Linsky, Harold, and Meleney, Henry E. The relation between spermatogenesis and leucopoiesis in acute infection 117

Liver, a case of acute yellow atrophy, with compensatory changes in the. E. Moschcowitz 54

Liver of rats, the experimental production of sarcoma of the. F. D. Bullock and M. R. Curtis 149

Loewe, Leo, and Strauss, Israel. Experimental studies in encephalitis lethargica 18

Lung, sarcoma of the, a case of. A. V. St. George 48

M

Mackenzie, George M. Precipitin formation in a patient with serum disease showing immediate and accelerated reactions 91

MacNeal, Ward J., and Cohen, Martin. Metastasis of carcinoma into an endothelioma of the optic sheath ... 145
Meleney, Henry E., and Linsky, Harold. The relation between spermatogenesis and leucopoiesis in acute infection 117
Meleney, Henry E., and Pappenheimer, Alwin M. Pathological findings in 17 cases of pneumonia during the influenza epidemic of January–February, 1920 56
Metastasis of carcinoma into an endothelioma of the optic sheath. Martin Cohen and Ward J. MacNeal 145
Moschcowitz, E. A case of acute yellow atrophy with compensatory changes in the liver 54
Muller, Henry R. Aneurysm of the hepatic and gastroduodenal arteries, with rupture of the aneurysm into the duodenum 46

O

Optic sheath, metastasis of carcinoma into an endothelioma of the. Martin Cohen and Ward J. MacNeal 145

P

Pappenheimer, Alwin M., and Meleney, Henry E. Pathological findings in 17 cases of pneumonia during the influenza epidemic of January–February, 1920 56
Pathology of Experimental Pneumonia. Russell L. Cecil 62
Pneumonia, experimental, the pathology of. Russell L. Cecil 62
Pneumonia, pathological findings in 17 cases of, during the influenza epidemic of January–February, 1920. Henry E. Meleney and Alwin M. Pappenheimer 56
Precipitin formation in a patient with serum disease showing immediate and accelerated reactions. George M. Mackenzie 91

Q

Quiescent metastatic gastric carcinoma. G. L. Rohdenburg.. 141

R

Relation between spermatogenesis and leucopoiesis in acute infection. Henry E. Meleney and Harold Linsky 117
Rohdenburg, G. L. The glycemic reaction, its clinical significance, and its relation to immunity 1
Rohdenburg, G. L. Quiescent metastatic gastric carcinoma 141
Rohdenburg, G. L. A tumor of the thymus gland 97

S

Sarcoma of the lung, a case of. A. V. St. George 48
Sarcoma, the experimental production of, of the liver of rats. F. D. Bullock and M. R. Curtis 149
Serum disease, precipitin formation in a patient with, showing immediate and accelerated reactions. George M. Mackenzie 91

Spermatogenesis and leucopoiesis, the relation between, in acute infection. Henry E. Meleney and Harold Linsky 117
Soletsky, David, and Zingher, Abraham. Besredka's method of oral immunization of rabbits with ox-bile and paratyphoid vaccine 133
St. George, A. V. A case of sarcoma of the lung 48
Stillman, Ralph G. Carcinoma of the bronchus with thrombosis of the superior vena cava 66
Strauss, Israel, and Loewe, Leo. Experimental studies in encephalitis lethargica 18
Syphilis, experimental. Wade H. Brown 99

T

Thymus gland, a tumor of the. G. L. Rohdenburg 97
Tumor of the thymus gland. G. L. Rohdenburg 97

V

Vitamines and the Avitaminoses. Casimir Funk 119

Z

Zingher, Abraham, and Soletsky, David. Besredka's method of oral immunization of rabbits with ox-bile and paratyphoid vaccine 133

PROCEEDINGS

OF THE

NEW YORK PATHOLOGICAL SOCIETY

NEW SERIES, VOLUME XXI

1921

SOC. PATHOLOG. NOV. EBORACI.
MORS GAUDET SUCCURRERE VITAE.
MORGAGNI
MDCCCXLIV.

Organized in 1844 Incorporated in 1886

NEW YORK
1921

PRESS OF
THE NEW ERA PRINTING COMPANY
LANCASTER, PA.

Proceedings

of the

New York Pathological Society

New Series, Vol. XXI JANUARY-MAY, 1921 Nos. 1-5

CONTENTS

PAGE

The Bacteriophage Reaction of d'Hérelle. *Abraham Zingher, M.D.* 2
Cutaneous Reactions in Human Hypersensitiveness. *Robert A. Cooke, M.D.* 8
Diffuse Endothelioma of Bone. *James Ewing, M.D.* 17
Chemical Changes in the Blood in Nephritis. *Victor C. Myers, Ph.D.* 25
Significant Chemical Changes in the Blood in the Toxemias of Pregnancy. *John A. Killian, Ph.D.* 29
Lipoma of the Uterus. *Robert C. Schleussner, M.D.* 33
Concerning a Phage (Lytic Agent) Isolated from Transplantable Animal Tumors. *George L. Rohdenburg, M.D.* 38
The Simultaneous Occurrence of a Metastasizing Hepatoma and an Epithelioma of the Esophagus. *De Witt Stetten, M.D.* 42
Demonstration of Leptospira Icteroides, with Notes of the Results of Prophylaxis and Serum Treatment of Yellow Fever. *Hideyo Noguchi, M.D.* 49
A Complement Fixation Test of Value in the Clinical Diagnosis of Toxic Thyroid States. *William N. Berkeley, M.D.* 51
Technique of Complement Fixation Reaction in Basedow's Disease. *John Koopman* 56
Probable Syphilitic Interstitial Pneumonia in an Adult. *Rolfe Floyd, M.D.* 58
Malignant Tumors of the Lung. *A. V. St. George, M.D.* 65
Three Brain Tumors. *Nathaniel B. Stanton, M.D.* 77
Fibrosarcoma of Appendix. *George L. Rohdenburg, M.D.* 83
A Tumor of the Left Auricle. *P. D. Hoffman, M.D.* 85
Two Cases of Congenital Lesions of the Heart. *Alexander Fraser, M.D.* 91
Typhoid Lesions of the Kidney. *Alexander Fraser, M.D.* 95
Hyperplasia of the Parathyroid Glands in Rickets. *John Minor, M.D., and A. M. Pappenheimer, M.D.* 90
Primary Bone Tumors: Their Classification with Special Reference to Benign Giant-Cell Tumor. *H. S. Martland, M.D.* 102
Primary Spindle-Cell Sarcoma of the Liver Associated with Cirrhosis. *Morton Ryder, M.D.* 113

A Reply to Dr. Johannes Fibiger on the Subject of Irritation Tumors. *Francis Carter Wood* 122

DR. DOUGLAS SYMMERS, *President*

THE BACTERIOPHAGE REACTION OF D'HÉRELLE

ABRAHAM ZINGHER, M.D.

The interesting studies published during the past three years by d'Hérelle,[1] Kabeshima,[2] Salimbeni,[3] Bordet and Ciuca,[4] Gratia,[5] and Maisin[6] have drawn our attention to an agent that seems to have an important function in the destruction of the intestinal bacteria and in the recovery from the diseases included in the typhoid-dysentery group. Such a bacteriophagic agent was originally described by Twort[7] in the *Lancet*, 1915, in connection with observations on *staphylococcus* cultures derived from glycerinated vaccine virus, and on *coli* cultures from the intestinal tract of dogs suffering from distemper. Similar observations were also made by him on a large bacillus obtained from the intestinal tract of children suffering from diarrhœa.

The agent is described by d'Hérelle as a filterable virus which grows upon and destroys the pathogenic bacteria with which it is associated. It is found toward convalescence in the intestinal diseases, is not absolutely specific, and can be cultured indefinitely in series by transplanting a fraction of a loopful of the lytic fluid into fresh suspensions of the bacteria in bouillon.

These observations were first carried out by d'Hérelle in connection with the Shiga dysentery and then extended to the other types of dysentery, to typhoid, paratyphoid, and fowl typhoid.

Kabeshima does not consider this agent as a living virus, but as a ferment derived originally through the action of a leucocytic catalyzer upon the bacteria, causing the liberation of a ferment which can continue to act indefinitely in series of fresh suspensions of the organism.

Salimbeni's observations indicate that we are dealing with a myxameba-like organism which has two stages—a filterable spore stage and a vegetative fungus stage. These observations are probably erroneous. The appearances, which he describes, are probably artefacts developing during different stages of lysis of the bacteria

More important, however, in explaining the nature of this agent is the work of Bordet and Ciuca, who consider that this lytic power is an hereditary lytic property produced by the action of leucocytic ferments upon bacteria, some of which subsequently acquire a property of being lytic for the original strain from which they were derived. Bordet and Ciuca obtained the lytic agent by the injection of a *B. coli* strain into the peritoneal cavity of guinea pigs. The action of this lytic peritoneal exudate upon the original strain showed up colonies of the *B. coli* which were resistant to lysis and very mucoid and translucent in appearance. The bacteria of this "modified" strain of *B. coli* were actively motile, resistant to the action of the lytic agent, and much more pathogenic for guinea pigs than the original strain. These "modified" bacteria have acquired the property of producing inhibition of growth and lysis of the original strain. This property is preserved through later generations and represents a new biological function of the bacteria.

One of Bordet's co-workers, Gratia, has shown more recently that in an old and evidently dead culture of the Bordet strain of *B. coli* small colonies were found that were markedly resistant to ageing. Upon transplantation these colonies proved to have the same resistant properties to the lytic agent as those of the resistant strain obtained directly by the action of the lytic fluid upon the original strain of *B. coli*. These studies, according to Gratia, seem to have an important bearing upon the questions of virulence, the heredity of acquired characteristics, and the formation of new races.

Through the kindness of Dr. Hardé, who brought specimens of lytic fluid from d'Hérelle to this country and placed them at my disposal, I was able to make some studies on the nature of this agent. The pressure of other work has prevented me from continuing these most interesting studies, and I can only submit the following limited observations:

One specimen marked "Bateriophage anti-Shiga," dated May 19, 1919, produced inhibition of growth in a fresh suspension of the Shiga bacillus and caused lysis of bouillon cultures grown

24 to 48 hours. Subcultures were sterile. A trace of this new lytic fluid showed the same property toward fresh bouillon suspensions, which in turn exerted the same powerful lytic action, which could be continued on indefinitely in series.

By great dilution the action of this lytic agent was diminished. In place of the complete inhibition of growth on the agar subcultures which were made immediately after the addition of the diluted lytic fluid to a fresh suspension of *B. Shiga*, a surface growth developed which showed here and there circular depressions with no growth surrounded by a halo leading off into the growth. These circular depressions were considered by d'Hérelle as representing colonies of the bacteriophage, by Gratia as the evidence of the lytic action of products of the resistant bacteria upon the non-resistant bacteria.

By making agar plates of the Shiga bacillus and streaking the surface crosswise with a loopful of the lytic fluid I could observe the following day a complete area of clearing along the path of the streaked lytic fluid which was surrounded by a regular surface culture of the Shiga bacillus. Studying the margin of the clear area, I noticed that the culture of the Shiga bacillus had at this point a shelving edge where it was quite translucent, and which upon microscopical examination showed the presence of most interesting structures. There was first a fine granular background, representing probably detritus derived from the bacteria; second, long, slender, refractive crystals, singly or in small groups of two and three; third, numerous irregular structures, not motile, pentagonal or hexagonal in shape, or of an irregular round form, which stood out clearly against the granular background. These bodies resemble closely in size and appearance crenated red blood cells. They could be floated in a hanging drop and seemed to have a somewhat spherical shape. They could be stained with Giemsa and less clearly with Gram's stain in ordinary preparations and in preparations made by impression from the agar plate. In the stained preparations the structures appeared as amorphous non-nucleated masses. It is probable that these structures represent *hyaline masses of protoplasm* resulting from the action of the lytic agent upon the bacteria. Here and there along the margin of the streak small circular indentations could be seen in the culture proper which corresponded closely in appearance to the colonies of bacteriophage described by d'Hérelle. The microscopical examination of the margins of the circular areas showed numerous structures similar to those described above—granular detritus, refractive, slender crystals, and irregular protoplasmic hyaline bodies. The more central part of the clear streaked area showed in places upon microscopical examination similar structures.

After two to three days there appeared in the clear area small colonies which upon transplantation grew with difficulty. On the agar plates the subcultures of these resistant colonies did not show the above-described structures which indicate the action of the lytic agent upon non-resistant bacteria.

The specificity of the lytic fluid was also studied. It was found to completely inhibit a second strain and only partly inhibit a third strain of *B. Shiga*, and to produce complete inhibition of a Flexner-Harris and a Mt. Desert strain of dysentery bacilli. It had no action upon a typhoid strain (Pfeiffer), *B. coli*, *B. sanguinarium*, and paratyphoid A and B.

Microscopical studies of hanging drops made according to the method described by Salimbeni gave no evidence that we are dealing with a myxameba. The irregular hyaline structures described previously showed no motility. The lytic agent was found to produce very active and almost instantaneous agglutination of bacteria.

The lytic agent resists the temperature of 70° C. for one half hour, but is partly destroyed by a temperature of 75° C. for one half hour.

Studies were also made with the anti-typhoid bacteriophage sent over by d'Hérelle. On the agar plates inoculated with the *B. typhosus* (Pfeiffer) and streaked crosswise with a loopful of the lytic fluid, structures similar to those described above were found along the margin of the culture and within the cleared area.

The anti-typhoid lytic fluid produced complete inhibition and lysis of the *B. typhosus* (Pfeiffer). It also produced complete inhibition and lysis of the Flexner-Harris and Shiga dysentery strain, but only partial inhibition and lysis of paratyphoid A and B strains, of five recently isolated typhoid strains, and of the Mt. Desert strain, and no lysis of the *B. coli* and *B. sanguinarium* strains.

A third bacteriophage against the *B. sanguinarium* was also studied. Structures similar to those described in connection with the anti-Shiga and anti-typhoid bacteriophage were also seen on plates inoculated with the *B. sanguinarium* and streaked crosswise with a loopful of the anti-sanguinarium lytic fluid. The lytic agent produced complete inhibition and lysis of three different strains of *B. sanguinarium*, of the Shiga strain, and of the typhoid (Pfeiffer) strain.

The foregoing short studies indicate that these lytic agents are not *absolutely specific* for their own bacterial strains. They also indicate that we can recognize the *lytic action* of these agents upon bacteria by the *curious irregular but sharply defined and prominent structures which are found on agar plates at the point of contact of the lytic agent and the bacterial culture—long, slender crystals and protoplasmic hyaline bodies.* A few small colonies developed slowly within the clear area on the streaked agar plates. Subcultures on agar showed that they were *resistant* to the action of the lytic agent. This was also seen when the lytic agent was added to fresh suspensions of these bacteria.

Bibliography

1 D'HÉRELLE, F.: *Compt. rend. Acad. d. sc.*, 1917, clxv, 373; 1918, clxvii, 970; 1919, clxviii, 631.
D'HÉRELLE, F.: *Compt. rend. Soc. de biol.*, 1918, lxxxi, 1160; 1920, lxxxiii, 52, 97, 247, 1318, 1320; 1921, lxxxiv, 339, 384, 538, 719, 863, 908.
2. KABESHIMA, T.: *Compt. rend. Soc. de biol.*, 1920, lxxxiii, 219, 471.
3. SALIMBENI: *Compt. rend. Soc. de biol.*, 1920, lxxxiii, 1545.
4 BORDET AND CIUCA: *Compt. rend. Soc. de biol.*, 1920, lxxxiii, 1293, 1296; 1921, lxxxiv, 276, 278, 280, 745, 747, 748.
5. GRATIA, A.: *Compt. rend. Soc. de biol.*, 1920, lxxxiv, 275, 750, 751, 753, 755; 1921, lxxxv, 25. *Jour. Exper. Med.*, 1921, xxxiv, 115.
6. MAISIN, J.: *Compt. rend. Soc. de biol.*, 1921, lxxxiv, 467, 468, 755, 847.
7 TWORT, F. W.: *The Lancet*, 1915, ii, 1241.

Discussion:

DR. WILLIAMS: I have followed Dr. Zingher's work with a great deal of interest. The macroscopic appearance in these plates of rounded chewed-out areas is very similar to the appearance that can be obtained when inoculating amebas with cultures of suitable bacteria, such as *B. dysenteriæ* or *B. typhi.* But under the microscope these appearances are nothing like those of any amebas I have ever seen. These small ameboid-like bodies look much more to me like broken down products than like living organisms.

DR. PARK: This paper deals with a subject which is both most interesting and most difficult of understanding. I think it must appear to all of us that it is almost impossible to conceive that the results are due to ferments alone since we do not know anything about a ferment which may increase. Again the idea that a microorganism would suddenly so change its function as to make a ferment which would attack the strain from which it had lately developed is something that we have never come across, so that naturally the newest hypothesis of Salimbeni that there is a parasite growing on the organism appealed very much to us. This theory has its own difficulties. If the parasitic fungi exist there must be a number of these. We are exploring in a new field which is very interesting. It is hazardous at the moment to say more than that.

MISS KUTTNER: I have been able to isolate a lytic principle similar to that described by d'Hérelle from a typhoid stool sent to me through the courtesy of the Health Department. It corresponds to practically everything d'Hérelle has described. It is non-specific; it acts on the homologous typhoid strain and on the other typhoid strains, as well as on Shiga and Mr. Desert dysentery bacilli. It has no action against paratyphoid A or B, or against *B. coli.* It is both inhibitory and lytic. I have not found that cultures dissolved or inhibited by this lytic principle remain sterile indefinitely as described by d'Hérelle. If cultures which have been acted upon by the lytic principle are plated after several days two types of colonies develop, one the typical round typhoid colony, the other irregular. The irregular colonies are often quite jagged and triangular, and if transplanted into broth do not make the broth turbid, whereas a normal colony from the same plate does, and furthermore, the lytic principle is also transmissible from one of these colonies fished into broth, that is, starting with a fishing of one of these triangular colonies in broth, the lytic principle can be transmitted in series in the same way as from the original stool filtrate. I would like to ask Dr. Zingher how he reconciles the theory of the ultra-microscopic spore with the fact that a single brief contact with this lytic principle changes the organism so as to give two types of colonies from one of which it is possible to transmit the lytic principle in series. For instance, if a small amount of the lytic principle I have isolated from a typhoid stool is added to a young turbid broth culture of typhoid, Shiga or Mt. Desert, and sub-cultures are immediately made, it will often be found that the two types of colonies, the normal and the lytic, will be obtained. I cannot understand how a single short contact with the lytic principle in this way, which produces such an immediate and profound change in the cultures of three different organisms such as typhoid, Shiga and Mt. Desert, can be attributed to the action of a fungus.

Dr. Jobling: It is difficult to assign the phenomena described by Dr. Zingher to the action of either bacteria, fungi, or antibodies. The fact that Bordet was able to obtain a similar agent from bacteria after their injection into the peritoneal cavity of a guinea-pig complicates matters. Is the agent producing the lysis a normal inhabitant of the peritoneal cavity, or was Bordet fortunate in his choice of a guinea-pig? Are we to assume that there is in the intestine a specific substance, or organism, for each type of bacillus; or are we to believe that the agent exists free in the intestine, with the ability to become attached to any organism after which it cannot grow except in symbiosis with that particular organism?

Dr. Zingher: I have not been able to confirm the observation of Salimbeni as regards the myxameba-like structures which he has observed in wet slide preparations of bacterial suspension and lytic agent. The small, highly refractile bodies which he describes in hanging drops of a freshly made preparation of bacteria and lytic agent seem to be simply the ends of bacteria, which are seen in a vertical instead of a horizontal position. I have noted the two types of colonies of which Miss Kuttner spoke. The irregular colonies show upon microscopic study the structures characteristic of the action of the lytic agent upon the bacteria—the long slender crystals and the sharply defined irregular hyaline masses.

CUTANEOUS REACTIONS IN HUMAN HYPERSENSITIVENESS

ROBERT A. COOKE, M.D.

(From the Department of Immunology of Cornell University and the New York Hospital, First Medical Division)

The two main points that I shall discuss with you regarding the cutaneous reaction in human hypersensitiveness are first the method of making the test and secondly the significance of the local reaction.

1. *Method of Testing:* Cutaneous tests can be made by the abrasion method when the substance to be tested is applied in dry form or as an extract, or by the intradermal method when a solution or extract is introduced into the skin by means of a fine hypodermic needle.

Dr. Brown has been making some very careful duplicate tests with these two methods in our clinic, and since time will not permit a detailed statement, I shall only say that the results warrant the conclusion that the intradermal test is by far the more delicate and gives definite positive results to agents definitely proven to be productive of clinical symptoms when the abrasion test, using these same agents, is absolutely negative. What follows has to do entirely with results from the use of the intradermal test and our own preparations.

2. *Significance of the Cutaneous Reaction:* The *local reaction* divides itself into three groups, (1) the immediate reaction, (2) delayed reaction, (3) negative. The *immediate reactions* are marked, moderate or slight. Marked reactions are characterized by the appearance of an urticarial wheal with pseudopod projections and a surrounding zone of hyperemia, appearing in ten to fifteen minutes. Moderate reactions lack the pseudopod projections and do not form so large a wheal. They have a hyperemic zone. The slight reactions show a hyperemic zone with little or no increase in the wheal. Slight and moderate reactions are at times obtained to extracts in a very weak solution and become marked where more concentrated solutions are tried. Where reactions are slight or moderate to the concentrated extracts they are dismissed as of no clinical significance unless they go on to develop delayed reactions and fall then into a different group to be discussed later.

Marked reactions are of the greatest importance, but they, too, are occasionally false. At times one gets what we call the "splash" reaction, when the point of the needle happens to lie between two easily separated layers of the derma or epiderma, and the extract seems to splash out at once into an area with irregular edges. In such cases the wheal looks like a marked positive reaction, but it lacks the hyperemic zone. This also happens when an air bubble is introduced by mistake. Then occasionally, but not frequently, a definite marked positive reaction is obtained, which can never be verified. These, too, must be set aside as of no clinical significance, for they could only indicate a short fleeting phase of allergy, a clinical condition of which we are not as yet cognizant. But marked positive reactions occurring on repeated testings always indicate a true hypersensitiveness. This statement requires a reservation, or more truly an explanation, in order not to be misleading. Cutaneous hypersensitiveness does not necessarily indicate clinical hypersensitiveness, because in the ordinary course of life the allergen can never be brought in contact with the hypersensitive cells. Let me cite briefly two actual cases to illustrate the point:

The first is the case of a man forty-five years old who had been troubled for five years with a very extreme degree of vasomotor rhinitis, so-called. He gave marked cutaneous, ophthalmic and nasal reactions to corn and cottonseed meal. On the strength of this reaction one might have been tempted to withdraw corn and cornmeal from his diet. But it so happened that five years before this man had retired to a little farm and took great pride in his chickens which he fed himself religiously twice a day with corn and cottonseed meal. As soon as he stopped this his vasomotor rhinitis stopped. He was able to eat corn and cornmeal which he did freely as a test without the slightest trouble. An injection of extract of corn produced a constitutional reaction with coryza and cutaneous hyperemia and urticaria. This case also illustrates the dangers in the interpretation of positive reactions when applied to foods.

The other case is that of a woman thirty years of age who had never had hay fever of the early type, in May and June, and would have recognized it before because she had autumnal hay fever for about fifteen years. The test with a timothy pollen extract in March was markedly positive. That following June she had perfectly typical clinical hay fever of the early type.

We now have records of several such cases giving marked positive cutaneous reactions with negative ophthalmic reactions. Such cases we consider as potential hay-fever cases. They have no clinical symptoms because the mucous membranes have not become hypersensitive. But we have had the satisfaction of watching such cases develop clinical hay fever at a later date, at which time the mucous membranes react positively. Aside from the inheritance factor, such an experience tends to make one feel that the constitutional reaction is developed within the body by some means other than ordinary immunological procedure adopted in animal anaphylaxis.

Delayed cutaneous reactions occur from six to twenty-four hours after the test and are characterized by an area of edema and redness, usually with itching, sometimes only an inch or two in diameter, and at others extending to the elbow or even wrist when injection is made in the upper third of the arm. Of the clinical significance of such reactions nothing definite can be said at the present time. They are usually obtained with the food extracts rather than pollen extracts, and may occur in apparently normal individuals or in those with clinical asthma, urticaria or angio-neurotic edema; but so far as we can determine, foods giving such reactions may be eaten with impunity. We have never yet been able to make and prove a diagnosis on the basis of a delayed reaction, no matter how severe.

Negative Reactions: At the site of the test there is no enlargement of the papule caused by the injection of the 1/50–1/100 c.c. of the extract tested. There is no hyperemia or other evidence of cellular or vascular activity either immediate or delayed. In general such tests indicate absence of hypersensitiveness, at least in the skin. But in exceptional cases negative reactions occur when the clinical history is absolute and definite. We have seen a number of cases with a history of acute and severe abdominal pain, vomiting and diarrhœa, occurring about twenty minutes after the ingestion of clam. It has occurred not once, but several times. The cutaneous reaction is always negative. Such cases can readily be explained on the basis of a localization of the hypersensitive area to the gastric or upper intestinal tract. We have observed this same localization of hypersensitiveness to the nasal mucous membrane in a very few cases of vasomotor rhinitis, and not infrequently in hay fever the degree of hypersensitiveness is much greater in one eye than in the other.

Just as we see local reactions of the immediate and delayed type, so also do we see immediate and delayed clinical reactions. By delayed clinical reactions I mean a reaction occurring twenty-four hours to five days after the ingestion of a substance. Immediate local reactions, when they signify anything at all, indicate an immediate clinical reaction, but delayed local reactions are not indicative of delayed clinical reactions; in fact, they have no known significance.

Time has not permitted me to go extensively into details nor to give statistics on the relative frequency of the exceptions to the rule. Suffice it to say that the application of the test to the diagnosis of clinical condition must be made with the greatest care, and we make it a rule for the absolute diagnosis of a specific etiologic factor to conform to the following commonsense requirements, which we have dignified by the term postulates:

1. Hypersensitiveness must be proven either by:

(*a*) A local reaction of a marked type that can be verified at will, or by

(*b*) A constitutional reaction that duplicates the clinical condition under study when the allergen is introduced by ingestion, inhalation, or by intradermal, subcutaneous, or intravenous injection.

2. It must be proven that the individual comes in contact with the reacting substance in such a way that it can be responsible for the clinical condition.

Dr. George M. Mackenzie read a paper entitled "The Relation of Antigen and Antibody to Serum Disease Susceptibility and Insusceptibility," which appeared in *The Journal of Experimental Medicine*, 1921, xxxiii.

Discussion:

DR. LONGCOPE: I have naturally been very much interested in this work of Dr. MacKenzie's. Serum disease, which is really a characteristic example of an acute infectious disease, offers a beautiful opportunity to study certain phases of the relationship of an infecting agent to antibody formation in a condition where the cause of the disease is not a living agent, but one with physical properties only. For protein is not a living agent. The experiments which Dr. MacKenzie has described I think offer very good evidence that there is an essential difference between the susceptible individual and the insusceptible individual to this disease produced by the non-viable substance, horse-serum—that the susceptible individual does readily produce antibodies and precipitins, whereas the insusceptible individuals are not likely to produce antibodies, while in them the antigen, the horse-serum, continues to circulate as a perfectly innocuous substance for long periods of time. Dr. MacKenzie has discussed the possible explanation for these phenomena. I do not think there is any evidence to show that one explanation is better than another, but any observations or any data that can be brought to bear on the subject of individual susceptibility to disease are most important, and for that particular reason possible analogies are interesting, though it may not be proper to draw analogies for acute infectious diseases from these experiments.

In regard to Dr. Cooke's interesting observations, I am sure that Dr. MacKenzie has noticed that the intradermal tests were much more delicate than the dermal tests. Walker has ruled out the intradermal test, saying that it is difficult to read. I do not believe that there is any great difficulty in this regard, if the tests can be done with materials that are sufficiently diluted.

Dr. Cooke's observations on the reactions in the skin and in the mucous membranes, and their variation in the same individual to the same substance, are very interesting. We have noticed this a number of times, and I recall one man in particular who gave skin reactions to a great variety of substances. He was perfectly well when he was in the hospital, but whenever he left the hospital he was likely in a short time to have such a violent attack of asthma that he would be picked up in the street and taken to the accident ward of a hospital as a medical emergency. Among other things he gave a marked reaction to rabbits' serum, though he was perfectly certain that no animal ever gave him attacks of asthma. He said he could pet a rabbit and do anything he wanted to with it without danger of asthma. We took him into a room where a rabbit was. He touched the rabbit with his hand. Almost immediately he had an urticaria of the hand, and for a week subsequently he suffered from a terrific attack of asthma. Though he gave the same skin reaction to various other animal sera, he could be fed enormous quantities of dried serum without any disturbance whatsoever.

Another interesting thing is the varying degree of hypersensitiveness which great groups of individuals show. I have no doubt that if one selected a hundred or a thousand perfectly normal individuals that a good many of them would either give delayed or immediate reactions to certain protein substances. I give reactions to a certain number, and I have never had any symptoms from eating or coming in contact with any of these materials. There must be a variation in groups of individuals from those who are hypersensitive and who have symptoms which can be accounted for by this curious condition, through individuals who are rarely affected and finally to individuals who are perfectly normal, though still presenting evidences of hypersensitiveness when tested appropriately.

A confusing thing in interpreting the skin reaction is the frequency of multiple reactions. People who do have urticaria, asthma, etc., may react to a long series of substances, and we have seen a number of individuals who give extremely marked reactions to extracts of animal hairs, and yet in whom it is evident that the asthma is not brought on by inhalation of dust from these animals. I recall one boy in particular. From the strongly positive test we assumed that it was due to contact with some animal, until we discovered from his mother that she thought eggs had something to do with it. He gave no reaction to eggs, by the ordinary tests, but when given large quantities of egg intradermally, he did give a fairly marked reaction to it, and when eggs were removed from his diet, he recovered and has remained perfectly well for several years, except for one or two attacks following the ingestion of eggs. This is simply an illustration of the difficulty of analyzing the significance of skin reactions when many positive tests are obtained.

Dr. Huntoon: I think from Dr. MacKenzie's paper that he does not make a distinction in classification between those people who give immediate reactions, and who give typical serum disease which comes on five to twelve days after the injection of the serum. I believe he stated that the hypersensitive cases stood at one end of the line, and the cases that give no reaction at all at the other, and there are all gradations in between. If this hypothesis is true that these two classes of symptoms belong in the same class, then these individuals should show a considerable amount of precipitin in their blood before the serum is injected, and in that event the cases that give extensive immediate reactions with small amounts of serum would later show a typical serum disease. I wish Dr. MacKenzie would inform me on these points.

Dr. Park: I was going to ask Dr. MacKenzie concerning the point brought up by Dr. Huntoon. Dr. Cooke's observations seemed to indicate a difference in significance between the early and late reactions, while those of Dr. MacKenzie seemed to class them together. His observations are of great interest and value, even if his interpretation of their meaning may later have to be modified. Dr. MacKenzie attributes the serum reaction largely to the patient's characteristics. I wonder how he explains the differences in the sera from different horses. Most sera used in treatment are mixtures from different horses. In order to estimate the individual characteristics we used individual horse serums and found the serum from some horses gave very different reactions from that from others. I remember that No. 83 gave about sixty per cent. of scarlitiniform reactions and had to be discarded. There is certainly a marked difference in the sera as well as in the patients. Realizing that proteins giving the therapeutic effects were not necessarily deleterious, we tried to modify or select the serum so as to avoid the unnecessary reactions such as the immediate chill following an intravenous injection. We have met with some peculiar as well as interesting results. We found for instance that we had a slightly turbid antitoxin globular preparation which gave chills in about twenty-five per cent. of the cases injected. We filtered this and while perfectly clear it gave no chills, so we thought that by chance we had come upon the explanation. The next slightly turbid preparation we treated the same way, but without preventing the chills. What was more peculiar was that the good preparation was mixed serum from horses A and B, and the poor preparation was from horse B only. We now have a preparation which has become hazy and yet produces no chills, so that we see there is an unknown factor in the serum as well as in the patient, and that substances in one serum may inhibit the action of those in another. I believe there must be a difference between what causes a delayed and an immediate reaction.

Mrs. Parker: In regard to Dr. Cooke's observation that he and Dr. Coca were not able to prove that pollen is antigenic, I wish to say that I have been able to show that alkaline extracts of ragweed pollen have definite antigenic properties as shown by the Dale method. At the present time I am sensitizing a series of guinea pigs in order to determine whether they can be made generally anaphylactic to pollen. Since the Dale method is the more delicate test and since it proves that pollen is antigenic I thought it worth while to report the fact that I have obtained positive results with this method.

Dr. Berger: Is it possible by means of the skin test to tell whether a patient is partially or to a marked degree desensitized after treatment with pollen extract or any antigen? Dr. Schloss reported a series of cases last June in which he fed egg-white to infants. If the patient developed urticaria following the ingestion of egg-white he noticed that while the urticaria was present the skin test was negative or reduced. He reported several cases where the skin reaction was markedly reduced during an attack of asthma. Is the skin sensitive to bacteria? If the patient has accompanying his asthma a bacterial infection of the chest would the skin be an index of sensitiveness to the bacteria? I would like to know if the various bacterial extracts which are on the market are of any value. The difficulty I have found with the intradermal method is to get an extract of horse dander or cat hair into solution. You can obtain a dehydrated product which comes in solid form and which has to be diluted with sodium hydroxide and subsequently neutralized with acid. I wonder whether that product is the one Dr. Cooke used, or did he use a suspension of the dander in saline or water.

Dr. MacKenzie: In regard to the question raised by Dr. Huntoon, I evidently did not make myself clear that at the time the serum was administered to these patients only one was hypersensitive to horse serum. All the others were normal people with negative skin reactions. Last year before this Society I showed the curves of antigen and antibody in the circulation for the individual who was hypersensitive at the time serum was administered. He showed immediate and accelerated reactions. In him the antibody production was also earlier. He had not only an accelerated symptomatic reaction, but an accelerated antibody formation. All the other individuals in this series were not hypersensitive to horse serum at the time it was first administered. The susceptibility refers to the susceptibility to serum disease.

As to the error in technique, I did not wish to take up much time in the paper to speak of it. In one individual there was a severe serum reaction and a high titer of precipitin. If he had conformed with the other members of the series, the precipitinogen should have disappeared with the rise of the precipitin to a high titer, but it did not. That patient was studied before we realized the importance of testing the anti-horse serum for traces of antigen, and it was possible that the patient's serum containing an abundance of antibody was precipitating traces of antigen in the anti-horse rabbit serum we were using.

As to the differences in sera which Dr. Park spoke of, I cannot say anything with accuracy on that, because I have not tabulated the cases according to what serum was used in any particular individual, but we have used only serum from the Rockefeller Institute and from the Department of Health. I am not sure just how many cases in the series were treated with one or the other serum.

Dr. Cooke: In reference to Dr. MacKenzie's paper, I would like to say that if he can throw any light on the question of serum disease it is going to be a great help in the study of these delayed clinical reactions we see to-day.

I am also interested to know from Mrs. Parker that she has been able to demonstrate the antigenic properties of the pollen extract. Experiments of Coca, Flood and myself two years ago failed to show any antibody formation to ragweed pollen extract by the usual guinea-pig experiment.

There were a few questions as regards desensitization. When one injects hay fever patients with pollen extracts there is a decrease in the sensitiveness of the mucous membrane, but very little difference in the intradermal reaction. If there is any difference in the cutaneous reaction at all there is a tendency to disappearance of the itching which is usually a very marked manifestation of the reaction.

In the case of allergic children one has to be very careful in making any statement that what is being done in the way of injection or feeding has any effect on the course of the disease, because there is a tendency in all children to lose, naturally, the hypersensitive reaction to foods when this hypersensitiveness existed early in life, for in such cases it usually disappears from the eighth to the tenth year, at which time, although cutaneous reactions may or may not be present, the clinical reaction on the ingestion of the particular food has entirely disappeared. This is not due to any treatment. It is not due to injections or to feeding, because most of these children lose their hypersensitiveness when the specific food has never been eaten or injected. It is a natural phenomenon.

With regard to the bacterial proteins and sensitization, it is very difficult to say much. So far, using solutions of various bacterial proteins, we have never yet been able to get an immediate marked positive reaction that looked at all like the immediate reactions one gets with foods and pollen extracts, and furthermore, such reactions as do occur do not correspond to the bacteria that are isolated from the bronchial tract or from the nasopharynx. The whole question of bacterial hypersensitiveness is one about which we know very little at the present time.

There was one other question about the preparation of the extracts we used. One must always bear in mind that these reactions of necessity take place from some readily absorbable substance. It must be dissolved in the tears, or in the saliva, and be readily absorbable in order to get into contact with the cells. This being so, it is perfectly evident that when one speaks of getting reactions to cat hair or dog hair it is absolutely a misconception. What you do get reactions to are the epithelial cells that are attached, and the hair has nothing to do with the reaction at all. Solutions of dander of animals are readily obtained, and there is no trouble at all about dealing with an insoluble substance.

DIFFUSE ENDOTHELIOMA OF BONE

JAMES EWING, M.D.

For some years I have been encountering in material curetted from bone tumors a structure which differed markedly from that of osteogenic sarcoma, was not identical with any known form of myeloma, and which had to be designated by the vague term "round cell sarcoma" of unknown origin and nature. I had no opportunity of following the course or learning the outcome of these cases, as most of them were treated by amputation of the limb.

Recently a case came under observation at the Memorial Hospital which revealed that this tumor is highly susceptible to radium, a fact that convinced me that the disease was entirely different from osteogenic sarcoma, which resists treatment by the physical agents.

The story of this case is briefly as follows:

A fourteen-year-old girl had been treated by an outside physician in 1918 for nasal discharge and occasional bleeding. Some ocular symptoms led to the suggestion of congenital lues, and a Wassermann reaction being weakly positive, salvarsan was administered. In November, 1918, while pulling on a rope, a spontaneous fracture of the ulna occurred, followed by swelling which gradually subsided. In January, 1919, the swelling recurred and continued with pain and disability until a well-marked tumor occupied the upper part of the arm. This tumor was noted to fluctuate in size. The veins of the skin were dilated, and the appearance led to the diagnosis of osteogenic sarcoma. Eight injections of Coley's toxins were administered at Mount Sinai Hospital, without notable effect.

On April twelfth at the Memorial Hospital a radium pack of 12,760 millicurie hours was applied to the arm, and followed by two other packs at intervals of two weeks. The tumor began to recede at once and at the end of five weeks no external swelling remained.

On admission the radiograph showed a peculiar diffuse fading of the upper half of the shaft of the radius, and a faint line from the old fracture. The outline of the slightly swollen shaft was smooth (Fig. 1); there was no bone formation, no point of perforation, or area of erosion of the shaft, all of which features told against osteogenic sarcoma. The prompt recession

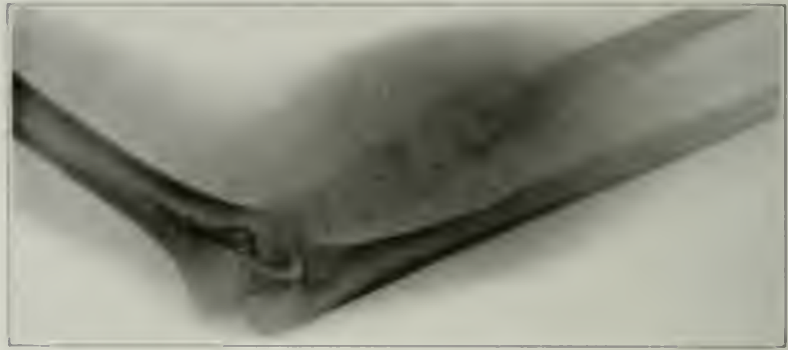


FIG. 1. Diffuse endothelioma of radius. Diffuse absorption of shaft; spontaneous fracture; invasion of soft parts.

under radium was also quite unlike our experience with osteogenic sarcoma (Fig. 2). With the recession of the tumor the shaft was well restored and normal function regained. The patient left the hospital with instructions to return weekly for observation, which was continued for several months.

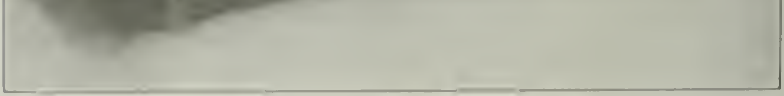


FIG. 2. Diffuse endothelioma of radius. After radium treatment.

The patient then came under the care of her original physician who noted persistence of the nasal and ocular symptoms, and, regarding the tumor of the radius as luetic, he instituted vigorous treatment by salvarsan. The injections, however, were followed by severe toxic symptoms, vomiting, bloody urine, collapse, and progressive anemia. Later injections of cacodylate of sodium were administered for the anemia. The patient failed steadily and the tumor of the arm began to reappear. There was now an irregular fever up to 103° F. The urine failed to show Bence-Jones protein.

In October, 1920, the patient returned to the Memorial Hospital with a definite recurrence of the tumor, and owing to the conflict of opinion, a portion of tissue was removed for diagnosis. It proved to be a round cell growth of the above-mentioned type. Other tumors had now appeared plainly in the skull. There was exophthalmos. The eye grounds showed choked disc and nerve atrophy. The radiograph of the lungs was negative. Anemia and cachexia progressed rapidly, and death occurred on December 23, 1920. The total duration was about thirty months.

During the past four months I have seen six other cases of this disease. They occurred in subjects from fourteen to nineteen years of age. The bones affected were tibia, ulna, ischium, parietal and scapula. The tumors grew rather slowly, requiring some months to attract attention, but they were accompanied by attacks of pain and disability. One boy complained only of intermittent attacks of pain after exercise during the summer, but in November a smooth swelling appeared over the upper half of the leg. Several tumors were found to fluctuate in size, a symptom due to their vascularity. All were rather painful and tender.

The radiographs give characteristic features on which a diagnosis may be based with considerable certainty. A large portion or the whole of the shaft is involved, but the ends are generally spared, contrary to the rule with osteogenic sarcoma. The shaft is slightly widened, but the main alteration is a gradual diffuse fading of the bone structure. Bone production has been entirely absent. Some of the bones appeared honeycombed. Perforation of the shaft and sharp limitation of the process are wanting. The central excavation with widened bony capsule, as seen in benign giant cell tumors, is missing. The radiograph is therefore rather specific.

Under radium treatment the tumor recedes and the shaft gradually becomes well defined with little deformity and no eccentric bone formation.

In seven cases the tissue was examined microscopically, and in all the structure was nearly identical. The growth was composed of broad sheets of small polyhedral cells with pale cytoplasm, small hyperchromatic nuclei, well-defined cell borders, and complete absence of intercellular material. Hydropic degeneration often affects large islands of cells, in which only nuclei and cell borders are visible. Necrosis occurred after radium applications. There is very little desmoplastic quality, but the tumor cells readily infiltrate muscle and pass along the fasciæ. In none were pulmonary or other forms of metastases observed. In the case cited the tumors of the skull were regarded as primary and of long standing. In some sections the cells were of increased size, while in others they were smaller and more compact, and approached the morphology of plasma cells. However, no definite areas of plasma cells have been seen in any case.

The probable endothelial nature of the tumor was suggested by the form of the cells, and especially by the appearance in broad

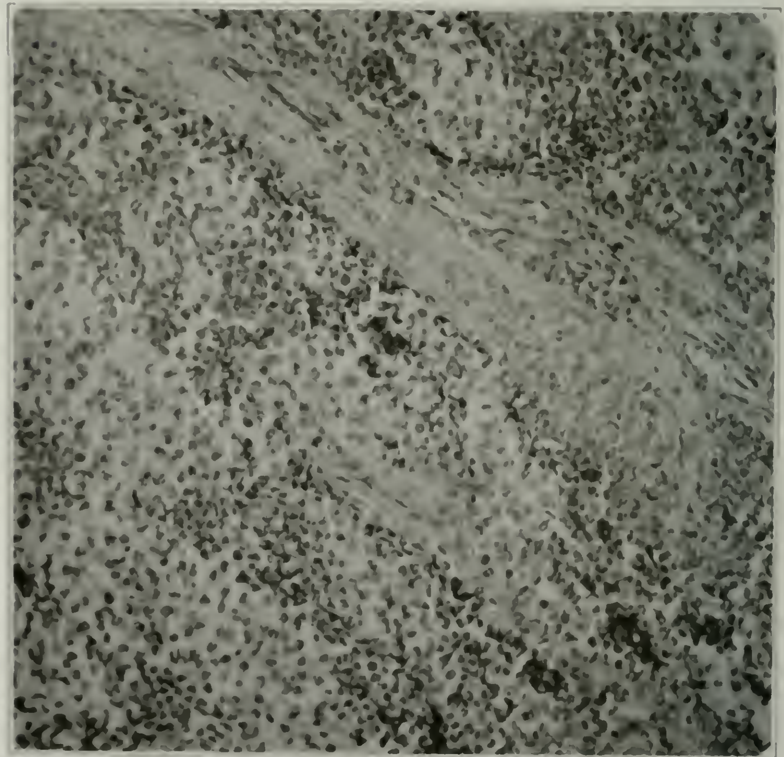


Fig. 3. Diffuse endothelioma of bone. Compact structure of large polyhedral cells.

sheets of polyhedral cells without intervening stroma (Fig. 3). This origin, however, did not seem to be fully supported until I encountered sections in one case in which the cells were found to line a complex series of fine channels inclosing intact blood (Fig. 4). Here the endothelial character of the cells was quite pronounced, but they were much smaller than those occurring in angio-endothelioma, with which this tumor is doubtless closely related. In other portions of the same growth the cells appeared in diffuse sheets without capillary lumina, as seen in the other tumors of the series.

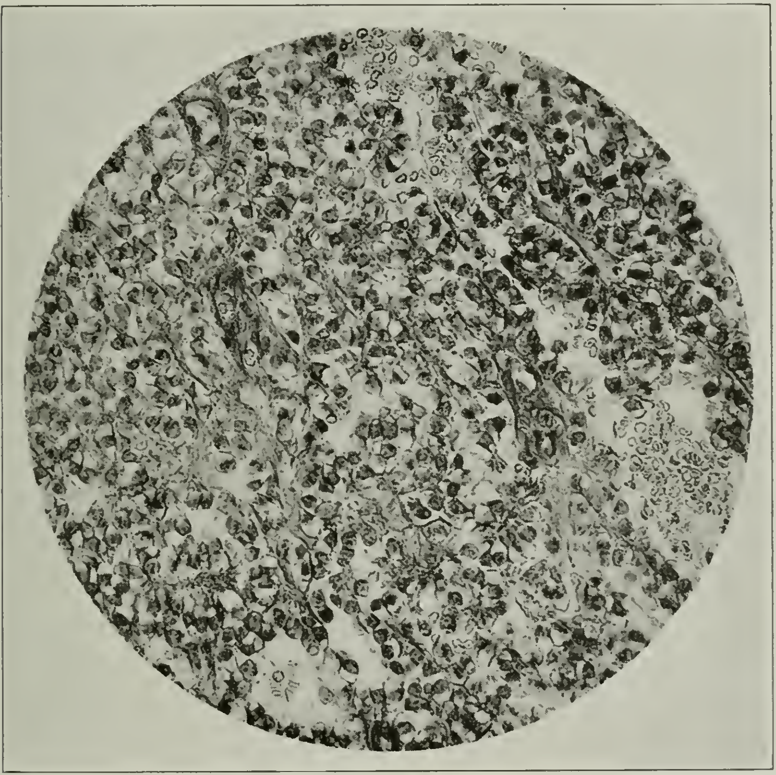


FIG. 4. Diffuse endothelioma of bone. Showing blood sinuses lined by tumor cells.

The exact point of origin of the growth is not clear, but the early rarefaction of the bone indicates that the disease begins in the blood vessels of the bone tissue. Yet an involvement, simultaneous or early, of the vessels of the bone marrow can not be excluded. In the discussions of multiple endothelioma in the literature some authors thought they could trace the origin to the vessels, blood or lymph, of the periosteum. Many multiple endotheliomas, as in Marckwald's case, have appeared well within the bone marrow.

The designation of the tumor as endothelioma rather than as myeloma seems advisable, since myeloma is properly reserved for tumors derived from the specific cells of bone marrow.

The possible relation of the endothelial tumor to plasma cell or other forms of multiple myeloma deserves consideration, but the evidence at present available indicates that the two processes are distinct. I have found no definite plasma cells in any of the specimens. Plasma-cell myeloma is nearly always multiple and often very widespread. Bence-Jones protein has not appeared in any of the cases of endothelioma, but is often absent in myeloma. Multiple myeloma also perforates the bone rapidly and destroys it completely, while these tumors cause slow, rather diffuse rarefaction.

A relation to the angio-endotheliomas and other forms of endothelioma, solitary and multiple, described in the literature, must be assumed to exist. Most of these tumors accessible in the literature have occurred in adults and were clearly recognized as endothelioma. All the tumors of the present series have occurred in children, and with one exception they have been solitary.

The main point of the present communication lies in the demonstration that there is a rather common tumor occurring in young subjects, commonly identified with osteogenic sarcoma, and usually called round cell sarcoma, which is really of endothelial origin, and which is marked by such peculiar gross anatomical, clincal, and therapeutic features as to constitute a specific neoplastic disease of bone.

Discussion:

Dr. Larkin: Dr. Ewing's contribution was such an illuminating one that I think a discussion of the study he has made of bone tumors for many years would be hardly possible in a short time. The idea which he has tried to give us of the endothelial origin of this class of tumors which we have been wont to regard as sarcomas for many years seems to be most convincing. If you look back at some of the cases which have been reported by a number of observers, I think that Dr. Ewing's ideas meet with the more radical views which we have of the conception of tumors. I believe that when you commence to look over a great many of your tumors which for many years have been classed as sarcomas that the more recent view of classifying them according to the genesis of the type of cells from which they spring will force us to accept Dr. Ewing's idea of the origin of this particular class of tumors. Not long ago Dr. Ewing reported a number of tumors in lymph nodes of endothelial origin. It was a notable contribution to pathological science, and I think that his views as expressed to-night represent the more modern view, so that we will have to look over and classify a good many of our bone tumors belonging in the class of angioendothelioma.

Dr. Moschcowitz: I would like to ask whether any oxidase stains were made on the sections, and I would like to know whether any metaplastic bone formation was noticed. It seemed to me in one of the lantern slides there were distinct shadows of new bone formation. This would perhaps make us skeptical in regard to accepting the endothelial interpretation.

Dr. Symmers: I should like to ask if there was any possibility of these individuals suffering from primary tumors of the kidney, notably the so-called hypernephromas, which often metastasize to bone, and the histology of which is not unlike that of the preparation thrown on the screen.

Dr. Ewing: I do not believe that any of the modern methods of determining biological differences of tumor cells were used. I do not consider them reliable differential signs and there are contributions in the recent literature which point out the uncertainty of these reactions in myeloma. Perhaps Dr. Martland will come to my help and tell you about his work on one of the cases.

In regard to metaplastic bone formation, if there were such metaplastic bone formation I think we should have to abandon our idea of an endothelial origin. That is one of the things the tumor does not show, and while this might be indicated as a possibility it certainly cannot be proven by X-ray plates, but only by microscopical study, and that study indicates the absence of such bone formation. In the gross specimen exhibited there are trabeculæ of bone at some distance from their original position which I think can be explained as mechanical displacements resulting from the growth of the tumor. The microscope shows that these trabeculæ are dissolving bone and not forming bone. The point which our President raises in regard to a primary tumor elsewhere has been the main question in the minds of those who are inclined to recognize endotheliomas in bone. I think in the angio-endotheliomas which are very destructive and which contain large blood vessels filled with blood, the cells do look like the large clear cells of the papillary carcinoma of the kidney, but in this tumor we have an entirely different type of cell, which I think Dr. Symmers would recognize as different from those of any tumor of the adrenal or kidney.

Another point is that these tumors occurred in young subjects, and there were no signs of malignant tumors elsewhere. One of the patients lived for two years. Renal tumors do not occur in young subjects of this type. I won't say they never occur, but that is not the age incidence of metastasizing clear-cell carcinoma of the kidney. It occurs in adults or older people. The age incidence is not so much against the origin of the angio-endotheliomas from renal tumors; angio-endotheliomas occur in adults. I would not offer a diagnosis of angio-endothelioma of bone in an adult without great care. Diffuse endotheliomas of children are different. I do not think the same suspicions surround them of possible metastatic origin that exist with the others.

Dr. Martland: Dr. Ewing's last case was a boy about seventeen years of age with a tumor on the parietal bone of two months' duration. We thought he might have multiple myeloma (Kahler's disease). Sections were stained for oxidase granules and were negative. He was examined very carefully for evidence of a primary growth elsewhere, especially to rule out hypernephroma or kidney tumor, and his skeleton was X-rayed for other growths with negative results.

I think Dr. Ewing has offered a distinct contribution to the pathology, diagnosis and treatment of malignant primary disease of bone, in calling attention to this type of lesion, because it has undoubtedly been diagnosed by most pathologists as osteogenic sarcoma.

Dr. Ewing states that these tumors are possibly amenable to radium treatment. In osteogenic sarcoma, especially the periosteal variety, amputation and resection have offered little hope (Bloodgood's series showing less than 4 per cent. of cures).

The treatment of malignant bone tumors is therefore so hopeless that it seems to me before any mutilating amputation or resection is performed an absolutely accurate diagnosis should be made. Such a diagnosis can in many instances be made from the X-ray in conjunction with the situation, age of patient, etc. But most cases, I believe, will require an exploratory operation to obtain an accurate diagnosis. The exploratory operation must be done under proper technique to prevent spreading of tumor, especially myxomatous tissue (cauterization with carbolic or actual cautery). If all means fail to make a diagnosis of malignancy, the tumor should be treated as a benign one.

CHEMICAL CHANGES IN THE BLOOD IN NEPHRITIS

VICTOR C. MYERS, PH.D.

(From the Laboratory of Pathological Chemistry, New York Post-Graduate Medical School and Hospital)

As is well known, the blood acts as the common carrier of food products to the tissues, and of waste products to the organs of excretion, and further aids in maintaining the neutrality of the body tissues and the normal osmotic relations. Oxygen, for example, is carried from the lungs to the tissues by the blood, while carbon dioxide is returned to the lungs for excretion by the same medium. Likewise the food nitrogen in the form of amino acids is transported by the blood to the various tissues, while the nitrogenous waste products, such as urea, uric acid and creatinine, are carried to the kidneys for excretion. The kidneys normally eliminate the end products of nitrogenous metabolism quickly and quite completely, so that in health they are never present in the blood in high concentration, but with impairment in renal function these substances may accumulate.

Normally the neutrality of the blood is maintained in considerable part by the blood bicarbonate. In acidosis, whether it be caused by the formation of β-hydroxybutyric acid as in diabetes or the non-elimination of acid phosphate as in nephritis, these acid substances combine with the bicarbonate, robbing the body of its alkali reserve, and thus lowering the CO_2 combining power of the blood.

The maintenance of the normal osmotic relations of the blood would appear to depend in large part upon the blood chlorides. In the so-called parenchymatous nephritis the ability to excrete the chlorides is impaired. To preserve the normal osmotic relations of the body fluids water is retained and edema results.

Usually the sugar of the blood is maintained at the very constant level of about 0.1 per cent., presumably through the glycogenic function of the liver, but in conditions of defective glycogen storage, with or without defective glucose oxidation, we have an increase in the blood sugar. When this exceeds the threshold level of about 0.15 to 0.18 per cent., the protective mechanism of the kidney allows the excess of sugar to escape into the urine. In so-called renal diabetes, however, this threshold is lowered, while in advanced diabetes, with renal complications, it is frequently raised. Nephritis is quite generally accompanied by a mild hyperglycemia.

From the foregoing it is apparent that kidney disease may result in a change in the blood content of such constituents as uric acid, urea, creatinine, CO_2, chlorides and sugar, in addition to many others. It should be borne in mind that the clinical symptoms of nephritis are the result of the pathological condition of the kidneys only indirectly, but rather the result of the accumulation of various products in the blood and tissues due to deficient kidney function.

How may blood analyses be used practically as an aid in the diagnosis, prognosis and treatment of renal disease? The function of the kidneys is to eliminate nitrogenous and other waste products from the body; consequently, a diagnosis based on the impairment in kidney function is especially useful, since it points the way to an intelligent treatment. The routine urine tests of specific gravity, protein, casts and blood cells are of considerable value in indicating the presence or absence of renal disease, but they furnish little information regarding renal function. It is for this reason that the blood tests are particularly useful, since they enable us to gauge the severity of the condition and formulate an opinion regarding the probable outcome. For example, a case may show a moderate amount of protein in the urine with a perfectly normal blood urea, and thus have a favorable prognosis, while another case may give a trace or even a negative test for protein, but have a high blood creatinine, indicating that a fatal outcome is a matter of only a few weeks or months. In the treatment of nephritis it will be conceded, I think, that dietary restriction in nitrogen or chlorides can be made intelligently only when a knowledge of the degree of impairment in the function of eliminating the nitrogen or chlorides is at hand.

There would appear to be little doubt that cases of incipient nephritis are accompanied by an appreciable rise in the blood uric acid, although a rise in the blood urea can probably be taken as a safer sign of impaired kidney function. It is certainly true that the urea nitrogen falls within very narrow limits for perfectly normal individuals. As soon as one passes to hospital patients, however, figures above 15 mg. of urea nitrogen are found. Figures over 20 on the usual restricted diet of the hospital would suggest impaired kidney function. Creatinine appears to be more readily eliminated than either uric acid or urea, and it is not, as a rule, until the blood urea has doubled, or more than doubled the normal, that there is a very appreciable increase in this purely endogenous waste product derived apparently from muscle metabolism. The normal for the creatinine of the blood is approximately 1 to 2 mg. per 100 c.c., and figures over 3.5 mg can be viewed with grave concern, while over 5 mg. are almost invariably indications of an early fatal termination. The only possible exceptions are cases where the retention is due to some acute renal condition, such as acute nephritis and mild bichloride poisoning.

Normally the CO_2 combining power of the blood plasma of the adult amounts to 55 to 75 c.c. per 100. In moderate acidosis figures between 30 and 40 are observed, while in severe acidosis the figures are below 30. All advanced cases of chronic nephritis suffer from acidosis, and in some cases this is apparently the cause of death. It may also be noted that cases of acute nephritis occasionally show marked acidosis.

In parenchymatous nephritis, if we may be allowed to use this term, the findings are quite different. Here the nitrogen retention is comparatively small, although the examination of the blood generally discloses a retention of chlorides. The figures for urea nitrogen seldom exceed 30 mg., except in the terminal stages of the disease, and generally fall between this figure and 15. The figures for chlorides, expressed as sodium chloride, frequently exceed 0.6 per cent. for whole blood and 0.7 per cent. for plasma.

It is of interest to note that many advanced cases of malignancy, possibly as a result of the toxemia, give the chemical blood picture of moderately severe nephritis; also that many cases of pneumonia show definite evidence of nitrogen retention; while in the terminal stages of the disease a severe acidosis quite generally develops, apparently as an indirect result of the marked arterial oxygen unsaturation of the blood.

Relatively high figures for the nitrogenous waste products are frequently noted in intestinal obstruction and lead poisoning, while a slight retention is often observed in gastric and duodenal ulcer, possibly for the same reason that retention is found in intestinal obstruction. The moderate nitrogen retention sometimes encountered in syphilis and certain cardiac conditions is apparently due to renal complications.

Since the blood findings in eclampsia are to be considered by Dr. Killian in the next paper, they will not be discussed here.

Kidney disorders, according to ordinary clinical groupings, give the following chemical blood pictures:

1. *Incipient nephritis:* Slight nitrogen retention (high uric acid, slightly elevated urea).

2. *Advanced chronic nephritis:* Marked nitrogen retention (including high creatinine), with or without severe acidosis.

3. *Acute nephritis:* (*a*) Mild,—moderate nitrogen retention; (*b*) severe,—moderate or marked nitrogen retention, with or without acidosis.

4. *Parenchymatous nephritis:* Slight or only moderate nitrogen retention, generally definite salt retention, occasionally marked hypercholesterolemia.

Although a diagnosis can best be made in connection with the full clinical history of the case, the findings of groups 2 and 4 are so typical as to allow in most instances of a diagnosis on the basis of the blood analysis alone. The terms employed above have been used solely with the idea of giving the different groups a simple name and without any anatomical significance.

A few illustrative cases which fall into the above groups are tabulated below:

Group	Uric Acid	Urea N	Creatinine	CO_2 Combining Power c.c. to 100	Chlorides as NaCl Per Cent.
	Mg. to 100 c.c. of Blood				
1..........	9.5	25	2.5		
2..........	7.7	200	26.7	12	
2..........	—	147	5.7	40	0.50
3..........	—	50	2.5	50	
3..........	11.2	93	5.9	54	
3..........	9.5	44	3.5	22	
4..........	2.3	28	1.9	56	0.70
4..........	4.5	22	2.1		Increased

Normal figures for the uric acid of the blood may be given as 2 to 3 mg. per 100 c.c., urea N 12 to 15 mg., creatinine 1 to 2 mg., CO_2 combining power 55 to 75 c.c. per 100 of plasma, and chloride of whole blood 0.45 to 0.50 per cent.

SIGNIFICANT CHEMICAL CHANGES IN THE BLOOD IN THE TOXEMIAS OF PREGNANCY

JOHN A. KILLIAN, PH.D.

(From the Laboratory of Pathological Chemistry, New York Post Graduate Medical School and Hospital, and the Department of Chemistry, Fordham University, N. Y.)

The first step in the study of the chemical changes involved in the toxemias of pregnancy was to determine whether in fairly comprehensive analyses of the blood a large group of representative toxic pregnant cases manifest any characteristic variations when compared with normal pregnant cases. The results obtained in this first step of the investigation are presented below, and, we believe, they admit of the deduction of definite conclusions.

At the outset it was evident that the toxic cases might be conveniently divided into three distinct groups:

1. Nephritic toxemias—including a group of cases that in their previous histories gave evidence of a preexisting nephritis which was not consequent to the pregnancy, but rather was aggravated by it.

2. Hepatic toxemias or true eclampsias—comprising cases that gave no evidence of preexisting impairment of renal function. By the clinical symptoms alone these cases can be readily differentiated from those of the former group.
3. Mixed toxemias—the cases within this group present evidence of a mild impairment of renal function which, however, resulted from the hepatic toxemias. The clinical findings alone are not sufficient to differentiate this group from group 2.

Four cases, carefully selected as normal pregnancies, showed low normal or slightly decreased figures for nonprotein nitrogen, with proportionately decreased urea nitrogen. The urea nitrogen formed from 45 to 50 per cent. of the nonprotein nitrogen. Uric acid, creatinine, chlorides and sugar proved to be normal, but the carbon dioxide combining power was slightly lowered. No hypertension was observed. The urine, on the other hand, from time to time contained traces of protein.

Four patients, all multiparæ, suffering from nephritic toxemias, were studied. Of these cases three showed impaired nitrogen excretion, whereas the fourth was a case of parenchymatous nephritis, with chloride retention. In the first three cases the nonprotein nitrogen was increased from 45 to 106 mg., the urea nitrogen in a similar manner was elevated from 28 to 72 mg., forming from 62 to 67 per cent. of the nonprotein nitrogen. The uric acid figures ranged from 4.8 to 8.1 mg., but the creatinine was only slightly increased. The fourth case showed no evidence of nitrogen retention, but the chloride concentration was considerably increased (0.52 per cent.) and was found to be associated with a marked edema. The decrease in the carbon dioxide combining power was not greater than in the normal cases. Large amounts of protein and occasionally casts were found in the urine. Further, these cases were characterized by a pronounced hypertension, and albuminuric retinitis with marked disturbance of visual acuity. Following the removal of the fœtus from the uterus, there was at most only a slight general improvement, with practically no return to normal in the chemical composition of the blood.

Twelve cases of hepatic toxemias or true eclampsias came under our observation, including two cases of pernicious vomiting and two cases of post-partum eclampsia. All of these cases were primiparæ save three, but the previous pregnancies of these three had also been toxic. In all instances a rise in the nonprotein nitrogen (34 to 56 mg.) was found; the urea nitrogen, on the contrary, was definitely decreased, constituting from 15 to 34 per cent. of the nonprotein nitrogen. The increase in the uric acid (3.5 to 11.0 mg.) was very striking. The greatest disproportion of urea nitrogen to the nonprotein nitrogen, the highest uric acid figures and the largest output of protein in the urine were found in the most toxic cases. This observed increase in uric acid, we believe, may be attributed to a renal irritation resulting from the toxemia, producing a slight impairment of kidney function.

No disturbance of the creatinine concentration of the blood was noted, but in the majority of cases there was a mild hyperglycemia and a pronounced decrease in the carbon dioxide combining power of the blood. In fact, two cases died of postoperative acidosis. A normal chloride concentration of the blood was found to be the rule, except in a few cases where high chloride figures were encountered in edematous patients. The protein excretion varied from a trace to a large amount. Although all cases had increased blood pressures, this elevation was not as pronounced as in the nephritic toxemias. Furthermore, unlike the nephritic toxemias, the cases in this group manifested a prompt improvement as judged by the chemical composition of the blood and as well by the clinical signs, following the removal of the fœtus from the uterus. Finally, no pathological changes were noted in the examination of the eye-grounds.

The mixed toxemias, apparently, represent a more severe degree of toxicity than the hepatic toxemias. The toxic factors in both groups of cases, no doubt, are identical, but in the latter it has produced a more severe impairment of renal function, resulting not only in the retention of uric acid, but likewise in a moderate accumulation of urea nitrogen. The nonprotein nitrogen was found to be from 56 to 64 mg., and although the urea nitrogen was considerably increased, nevertheless it formed but a small portion of the nonprotein nitrogen (32 to 38 per cent.). In this particular these cases differ from both the nephritic and hepatic toxemias; in other respects, however, they gave findings similar to the hepatic toxemias.

Dr. I. J. Levy read a paper on "The Relation of the Histopathology of the Kidney to Blood Nitrogen," which will appear in full elsewhere.

Discussion:

DR. MOSCHCOWITZ: Dr. Levy's presentation interested me enormously. I wish I possessed Dr. Levy's confidence in trying to partition out the various types of nephritis as he has done. For years I have been attempting to correlate function and anatomy in disease of the kidney and have been unable to predict the "type" of nephritis that will be found at autopsy from functional tests alone. It seems to me that such a prediction will resolve itself largely into a matter of guesswork. There are various reasons for this. The most important is the fact that in the past we have been regarding the "type" of nephritis as an end product. It seems to me rather that these "types" are not pure in the biological sense, but run into each other, and that they represent stages in a fairly well-defined pathogenesis beginning in an early glomerulo-nephritis and ending in the familiar contracted kidney. I refer now, of course, only to those kidneys that may be comprised under the term arterio-capillary fibrosis. The parenchymatous, the kidneys of subacute bacterial endocarditis, and the amyloid do not enter into this discussion. I propose to report shortly upon six autopsies in which marked evidences of nephritis were present during life, although at post-mortem the kidneys showed barely perceptible damage. On the other hand, all pathologists are familiar with the phenomenon of finding profoundly contracted kidneys at post-mortem although during life there were no evidences of nephritis. These patients died of something else. The point I wish to make clear is that clinical and anatomical nephritis are two entirely different things and can only be correlated in a very broad sense.

I have submitted in a number of papers the thesis that arterio-capillary fibrosis is a primary vascular disease. Whether the initial change is in the glomeruli or the terminal arterioles is not a matter of great consequence, although I believe it is in the former. All the changes that occur in such a kidney can be explained genetically from the progression of such early lesions. As Dr. Levy pointed out, the vast majority of patients with "nephritis" die a cardiac and not a renal death. They die of decompensation of the cardio-vascular apparatus just as patients do who have frank valvular disease. This is one of the reasons why it is so hard to interpret blood figures, such as Dr. Levy and Dr. Myers have presented, in terms of anatomy. Their greatest value, as Dr. Myers pointed out, is in estimating prognosis. The trouble with these figures in attempting an estimate of renal function is that they are dependent on too many extra-renal factors of which the most important are diet, water intake, the function of other viscera, the liver for instance, and myocardial insufficiency. The latter, in my opinion, is the most important factor. Non-nitrogenous retention seems to be proportional more directly to myocardiac insufficiency than to any other factor. I can confirm the findings of Rowntree and Geraghty, who showed both clinically and experimentally that tests for renal function depended largely upon the amount of chronic congestion of the viscera, a condition practically always present clinically and anatomically in nephritis. It is for this reason that a method of determining the volume output of the heart would be most desirable; unfortunately our instruments of precision afford no guide for the determination of this highly important function.

Dr. Schwarz: I should like to say a few words from the clinical standpoint, that we endeavor to get some of the types straight in our minds. I do not think we should look at this quite as darkly as Dr. Moschcowitz does, for observing these cases at the bedside there are certain distinct groups which are diagnosticated by the chemical examination of the blood. In the first group we find blood in the urine without an increased blood pressure, some reduction in the amount of urine excreted and some retention of the nitrogenous substances in the blood. These cases have an etiological factor—either scarlet fever or naso-pharyngeal conditions. These may or may not clear up and become chronic. The second group without any etiological factor but sometimes, however, due to diphtheria, has edema which is more or less persistent, no increased blood pressure, no retention of nitrogenous substances in the blood but a marked increased cholesterol in the blood. The third type not seen so frequently in children, but more often in adults, is always associated with hypertension and changes in the eyeground indicative of albuminuria retinitis, marked polyuria, polydypsia and low specific gravity, and is associated with scerotic changes in the kidney and no change in the blood chemistry.

LIPOMA OF THE UTERUS

ROBERT C. SCHLEUSSNER, M.D.

(From the Pathological Laboratory of the Lenox Hill Hospital, New York City)

In view of the infrequent occurrence of lipomata of the uterus, it was thought on encountering this case that it would be of interest to report it. Including the case here reported, there are but seventeen such tumors on record. Ellis quotes statistics of Williams, who found no case among 2,649 uterine tumors collected from four large London hospitals, and statistics of Gurlt, who encountered no case among 4,115 uterine tumors on record in the Vienna hospitals. In a review of the Index Medicus from 1890 through 1919 I found no case reported from New York City. This is the first case to occur among 14,500 operative specimens of all types examined at the Lenox Hill Hospital.

Of the seventeen cases on record, ten were collected from the literature by Seydel, who added a case of his own, in 1903. Pollack reported an additional case in 1903. Elkins and Haythorn in 1917 reported a case and enumerated the three cases reported in the interval between 1903 and 1917 by Ellis (1907), Sitzenfrey (1910), and Ley (1914).

The various case reports, with their comments, which were written from time to time as the tumors were encountered, cover quite comprehensively all that is known of the condition. This is particularly true of the paper written by Seydel, around whose paper the literature may be said to center. He reviewed critically all the literature to date, admitting to his list of cases only such as had been carefully investigated and described and definitely proven to be lipomata or lipomyomata. Knox in 1901 was the first one in recent years in this country to describe a case, though Schoinski in 1880 described a case which was accepted by Seydel.

Clinically there is nothing to distinguish these tumors from other non-malignant tumors of the uterus. It may be noted that the patients were for the most part from fifty to sixty years of age, though one patient with a cervical polypoid lipoma was but twenty-eight years old.

The tumors have varied both in their location and in the details of their structure. Four occurred as cervical polyps, the remaining thirteen as tumors of the body of the uterus. Seven, including the one here reported, are listed as simple lipomas. Of these seven tumors, two occurred as cervical polyps. The other ten tumors are classed as lipomyomas. These showed varying quantities of fibrous and smooth muscle tissue in the septa between the fat alveoli, while one tumor also showed sarcomatous areas. Of the ten lipomyomas two occurred as cervical polyps. The distinction between lipoma and lipomyoma is an arbitrary one and may vary with the viewpoint of the author. In general, it seems that the name lipoma has been applied to those tumors where the fatty tissue seemed to be sharply set off against the surrounding fibromuscular tissue and where no muscle strands entering the fatty tissue from the capsule have been evident. Those tumors, on the other hand, where the fibromuscular tissue has been seen very evidently to enter the fatty tissue from the capsule and disperse among the fat cells have been called myolipoma, or fibromyolipoma. But between the pure lipoma and the tumor, with thick strands of fibromuscular tissue entering the fat zone, there are all gradations. Thus in the tumor I shall describe the fibromuscular elements separating the alveoli of fat cells are barely to be distinguished at the periphery of the tumor. Taking the viewpoint that these fibromuscular strands are remnants of uterine tissue in the process of being pushed aside by he growing fat cells, I have classed the tumor as a simple lipoma. Perhaps it would be better to follow the lead of Elkins and Haythorn and refer to this entire group of tumors simply as "fatty tumors of the uterus."

Of the histogenesis of the fat cells occurring in these tumors nothing is known. The theories advanced are:

I. That they result from a fatty degeneration of the fibrous or muscular tissue in fibromyoma of the uterus. In support of this theory it has been urged that fatty degeneration has been observed in the muscle cells and connective tissue of these "fatty" tumors, and one author believed that he could trace the process in its various stages from beginning fatty degeneration to completed fat cell. This idea is contrary to present ideas of the specificity of tissue growth. Moreover, some of the tumors have shown no fatty degeneration whatsoever in their connective or muscular tissue.

II. That the fat cells arise by multiplication of fat cells congenitally misplaced.

III. That the fat cells arise by multiplication of fat cells brought into the uterus along with the blood vessels. Seydel quotes R. Meyer on this point, the latter stating that he has observed fatty tissue accompanying blood vessels into the uterus, though never deeply.

The case reported below occurred on the Gynecological Service of Dr. Oastler at the Lenox Hill Hospital:

The patient was a woman sixty years of age.

Family History: No significance.

Past History: No significance.

Menstrual History: Onset at thirteen years; last period fifteen years ago. No bleeding or discharge since.

Obstetrical History: One child thirty-five years ago, with normal delivery. No miscarriages.

Present Illness: The only symptom was pain in the left lower quadrant of the abdomen of four weeks' duration.

Physical Examination: General examination showed nothing of importance. Pelvic examination revealed a large tumor apparently connected with the uterus.

Working Diagnosis: Fibromyoma of the uterus.

Operation: A large tumor incorporated with the uterus was found lying in Douglas's pouch and bound to the adjacent viscera by adhesions. The entire mass was easily delivered and a supravaginal hysterectomy done.

The patient made an uneventful recovery.

Gross examination of the specimen reveals a tumor incorporated with the remnants of the uterus, and a tube and ovary. The tumor is roughly globular in shape and measures about five inches in diameter. In its growth it has distorted the uterus, so that its original position cannot be made out, but it can be seen that it has involved the body of the uterus and that it occupies an intramural position. On section the tumor has an almost uniform pale yellow color. A delicate connective tissue framework is present, but this forms a very inconspicuous part of the picture. The tumor is for the most part sharply marked off from the remnants of uterine wall which surround it, but in places strands of tissue merging with the uterine wall may be seen to enter the tumor proper and subdivide within it.

Microscopical examination shows the tumor made up for the greater part of mature fat cells arranged in bundles of various sizes and separated by strands of connective tissue showing various stages of hyaline degeneration. At the margin of the tumor it can be seen that the fat cells abut directly upon a wall showing connective and smooth muscle tissue. Both muscle and fibrous tissue may be demonstrated as components of the strands described in the gross as merging with the uterine wall and then subdividing as they enter the tumor. The thicker strands of fibromuscular tissue in the tumor and the fibromuscular tissue forming the capsule of the tumor are seen to contain fat cells in small groups or even isolated. It thus appears that there is no sharp line of demarcation between the fatty tumor and the remnants of uterine musculature present, though to be sure the invasion of the uterine wall by the fat cells is limited to the areas immediately adjacent to the tumor. This lack of sharp demarcation between the fatty tumor and the uterine wall has been described in other cases.

To me the most plausible interpretation of the above microscopic picture is that we are dealing with a lipoma of the uterus which in its growth has pushed aside the fibromuscular tissue, and that this latter tissue has then undergone degeneration. Certainly the fibromuscular tissue present does not suggest growth activity. For these reasons I have classed the tumor as a lipoma, though realizing that such a classification is open to criticism.

In concluding, I wish to thank Dr. Rohdenburg, who called my attention to the tumor and permitted me to report it from the laboratory.

Literature

Schoinski: *Chicago Med. Recorder*, 1880, vol. I (cited by Knox).

Seegar: *Ztschr. f. Wundartze u. Geburtsh.*, 1853, v, 24 (cited by Knox).

Smith: *Tr. Path. Soc., London*, 1861, xiii, 148 (cited by Knox).

Lobstein: Sur l'organisation de la matrice. Paris. 1803 (cited by Knox).

Meckel: Handbuch der Pathologischen Anatomie, vol. ii, 311 (cited by Knox).

Knox: Lipoma of the Uterus. *Bull. Johns Hopkins Hosp.*, 1901, xii, 318.

Brunings: Ueber Lipomyom des Uterus. *Verhandl. d. deutsch. Gesellsch. f. Gyn.*, 1899, viii, 348 (cited by Seydel).

Chiari: Lipofibromyom des Uterus, Verein Deutsche Aerzte in Prag. *München. med. Wchnschr.*, 1902, s. 946 (cited by Seydel).

v. Franque: Lipomyofibrom des Uterus. *Verhand. G. G.*, 1901, ix, 491 (cited by Seydel).

v. Jacobson: Zur Kentniss des Secundaren Veranderungen in der Fibromyomen des Uterus. *Ztschr. f. Heilk.*, Bd. 23, N. S. Bd. 3, *Abth. f. path. Anatomie*, 1902, s. 139, and *Ann. de gynec. et d'obst.*, Paris, 1902, lviii, 259 (cited by Seydel).

Lebert: Atlas der Anat. pathol., Pl. 16, Fig. II (cited by Seydel).

Merkel: Ueber lipombildung im Uterus. *Beitz. z. path. Anat. u. z. allg. path.*, 1901, xxix, 507 (cited by Seydel).

Orth: Lehrbuch der Spec. path. Anatomie, Bd. 2, s. 485 (cited by Seydel).

Wilms: Die Mischgeschwulste, Heft 1 and 2, Leipzig, 1899–1901 (cited by Seydel).

Seydel: Lipoma-fibromyomatosum Uteri. *Ztschr. f. Geburtsh. u. Gynäk.*, 1903, L, 274.

Walkoff: Ueber Liposarkombildung im Uterus. *Festschrift. f. Rindfleisch.*, 1907, pp. 212

Ellis: Lipoma of the Uterus. *Surg., Gynec., and Obst.*, 1906, 658.

Sitzenfrey: Intramuralis Lipomyosarcom der Vorderen Uterusward. *Ztschr. f. Geburtsh. u. Gynok.*, 1910, lxvii, 32.

Ley: Lipomatosis of a Fibromyoma of the Corpus Uteri. *Jour. Obst. and Gynec. Brit. Emp.*, 1914, xxv, 42.

Elkin and Haythorn: Fatty Tumors of the Uterus with a Report of a Case and Notes on Classification. *Surg., Gynec. and Obst.*, 1917, xxv, 72.

Pollack: *Wien. klin. Wchnschr.*, 1903, 68.

Discussion:

Dr. Wood: Small masses of fat are not uncommon in fibromyomata, but the appearance of a large discrete tumor of this type is a very great rarity. It seems to me that the most natural thing to assume is not that the tumors are formed by a degeneration of the muscle tissue, but are independent growths, possibly with a developmental basis.

Dr. Larkin: Seydel's article on this peculiar condition of the uterus is probably one of the best monographs which has been given to us on the pathology of this very rare condition. If I remember rightly his idea was that the fat was more or less of a metaplasia of connective tissue which might mass itself in a tumor formation or might occur in discrete areas in other uterine tumors, especially fibromyoma. I do not think he was wrong in his interpretation, because those who have had an opportunity of examining many fibromyoma find microscopically some conditions which seem to tend to fat transformation.

CONCERNING A PHAGE (LYTIC AGENT) ISOLATED FROM TRANSPLANTABLE ANIMAL TUMORS

G. L. ROHDENBURG, M.D.

(From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director)

Several years ago d'Hérelle announced that he had been able to isolate from the feces of those recovering from dysentery a substance which had the power of causing lysis of the etiological bacteria. Since that time there have been other publications dealing with various phases of the problem. D'Hérelle applied the term "phage" to the agent capable of causing this lysis.

Phages have been isolated from many sources by at least two technical methods. The phages which have been isolated from bacteria have been more or less specific in their lytic action. The nature of the phage is not yet fully determined. D'Hérelle is of the opinion that it is an ultramicroscopic organism, and the recent work of Salimbeni places the organism as a mycelium; Kabeshima, however, presents evidence which suggests the possibility of its being enzyme in nature. Since d'Hérelle was first able to isolate the lytic substance only from the feces of those recovering from the infection, he suggested that the phage might have something to do with convalescence.

Transplantable malignant tumors in animals are roughly divided into two groups, those which in varying percentage recede spontaneously and those which do not. In spite of many experiments, the cause of this spontaneous recession still remains unexplained. The experiments recorded in this report were undertaken with the idea that spontaneous recession of transplantable malignant tumors might possibly be due to a tissue phage.

The technical steps of the experiments are simple. The tissue to be examined is obtained under sterile conditions and a cube varying from 0.2 to 1 cm. in diameter is placed in broth. The inoculated tube is incubated for a period of forty-eight hours at 37° C. The presence or absence of a phage may be demonstrated by one of two methods. At the end of forty-eight hours' growth, if the broth remains clear, it is plated on nutrient agar, isolated drops of the broth being added to the agar plate just before solidification occurs. In a second method about 0.3 c.c. of the broth is added to a sterile two per cent. suspension of red cells in physiological saline. The agar plate, or the blood tube, are then incubated at 37° C. for twenty-four hours. The presence of a phage is predicated upon either the lysis of the red cells in the saline tube or definite zones of digestion in the agar plate (Fig. 1). If the original broth culture shows bacterial growth after incubation, then it should be filtered through a Berkefeld filter, and the clear filtrate used as previously described.

Following this technic, examinations of all of the twelve growing tumor strains in the laboratory were made. Each tumor strain was examined twice, and as controls, normal kidney, spleen, and fetal tissue were also examined. A phage was demonstrable in all.

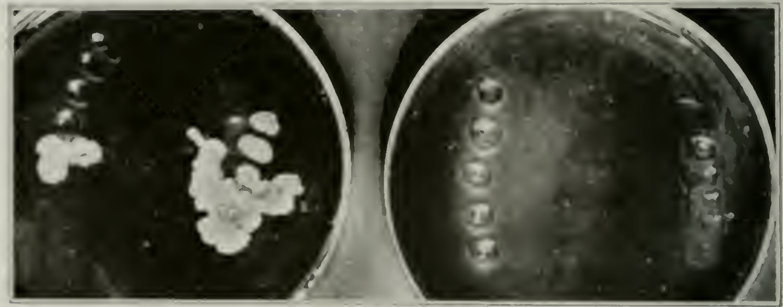


FIG. 1. FIG. 2.

FIG. 1. Pure phage isolated from transplantable animal tumor.
FIG. 2. Phage with intentional bacterial contamination.

The examinations were again undertaken with six receding tumor strains, actively receding tumors being cultured in each instance. A phage was demonstrable in all of twelve attempts. The same technic was then applied to a rapidly growing carcinoma of the breast in the human, and a phage was also isolated.

The following observations have been made on the phage isolated from receding rat and mice carcinomata and sarcomata: Lytic action of the broth culture is demonstrable up to a dilution of 1 : 1200. The phage can be propagated. The phage passes through a Berkefeld filter, but is not dialyzable through a celluloidin sac. Phage cultures to which red cells have been added show, after seven to fourteen days, a gradual reduction of the hemoglobin to some other pigment derivative. One strain of phage has been propagated for fourteen generations. The addition of alcohol or glacial acetic acid to the broth culture produces a copious flocculent precipitate, which is again partly soluble in physiological saline solution and which still shows phage action after twenty-four hours' contact with the precipitating chemical. The addition of blood to phage cultures has thus far uniformly resulted in a bacterial growth, the bacterium being a thin bacillus, occasionally occurring in chains, Gram-positive, and showing spores. This organism has not yet been identified; however, when it appears in a phage culture the lytic action of the broth very markedly decreases, or completely disappears. Contamination of phage culture by other bacteria, *i.e.*, staphylococcus, streptococcus, typhoid bacilli, *B. subtilis* and *proteus* does not inhibit or destroy the phage action.

A single injection of nonbacterial contaminated phage broth into animals bearing transplanted tumors which do not spontaneously recede does not cause recession, possibly because the blood present in the body brings about the development of the bacterial growth previously referred to. If any action be demonstrable, it is a stimulation of growth, though this can not be asserted positively. Animals bearing tumors which do not spontaneously recede when injected with the bacterial growth show no decrease in growth energy.

Discussion:

Dr. Noguchi: I would like to ask if you determined the optimum hydrogen ion concentration in which the phage acts.

Dr. MacNeal: I should like to know just what the action is on the agar. I take it these are agar plates to which a drop of this broth has been added. Apparently there is a hollowing out of the agar, and in some instances there seems to be a bubble of air in it. Of course these are formalin preparations, and it is difficult to tell what the original appearance may have been, or what is the interpretation of the change in the agar when it was fresh. Is it liquefaction, digestion of the agar, or what?

Dr. Wood: I would like to ask Dr. Rohdenburg to continue his argument a little further against or for a ferment. As far as my own opinions go, I watched the work with a great deal of interest, and I have not the slightest idea what the explanation is. I think we will have to suspend all judgment until more data have been collected. The phage evidently has nothing to do with the disappearance of tumors, because it is found in progressively growing tumors, and also in human tumors in which there is no possibility of regression.

Dr. Rohdenburg: These experiments are really only at their beginning, and no work has been done on the hydrogen ion concentration. I would add that the phage can be demonstrated by using 200 c.c. of salt solution to which 15 or 20 c.c. of ordinary nutrient broth and a fragment of tumor have been added.

The original appearance of the plates, when fresh, was perfectly smooth, and in those experiments where precipitation was obtained with acetic acid and alcohol, we could see, because of the precipitate, where the drop was placed. After twenty-four hours the surface of the agar was eroded. There was no liquefaction that was demonstrable, though the water of condensation on the plates might be due to the evaporation of the liquefied agar.

DR. MACNEAL: Did you drop the broth on before the agar was solidified?

DR. ROHLENBURG: Just before it was solidified.

THE SIMULTANEOUS OCCURRENCE OF A METASTASIZING HEPATOMA AND AN EPITHELIOMA OF THE ESOPHAGUS

DE WITT STETTEN, M.D.

Since the careful analysis by Harbitz[1] considerable interest has been shown by oncologists in the question of the simultaneous occurrence of multiple tumors—particularly of different neoplasms in diverse organs. It has recently been my fortune to have observed a rather unusual case of this nature, and it was with some trepidation—as I am only a surgeon—that I accepted your secretary's invitation to present this case before your Society.

The patient was a man, fifty-nine years of age. For about a year he had had vague abdominal symptoms, with loss of weight. Shortly before I saw him in October, 1920, he had had several attacks of pain, which resembled biliary colic. On examination, he was decidedly emaciated and a moderately enlarged, slightly nodular liver could be palpated. The gall bladder region was sensitive. There was no jaundice, nor temperature. The blood showed a moderate secondary anemia. The Wassermann test was negative. Radiography showed indirect evidence of gall bladder disease.

The probable diagnosis of carcinoma of the liver was made, but in view of the gall bladder symptoms, and the possibility of an error in diagnosis, an exploratory laparotomy was advised and performed on October 14, 1920. The liver was found diffusely enlarged, the surface was somewhat nodular and irregular in consistency, but it was difficult to find distinct nodes. The liver surface did not suggest a typical carcinoma. One small, definite nodule, lighter in color than the rest of the liver surface, and situated near the liver edge, to the left of the suspensory ligament, was excised for diagnosis. The gall bladder was found to contain numerous calculi and a cholecystectomy was done. The quadrate lobe felt particularly hard. There was no evidence of a primary growth in the stomach, gall bladder or intestines. There were fine adhesions between the upper surface of the liver and diaphragm.

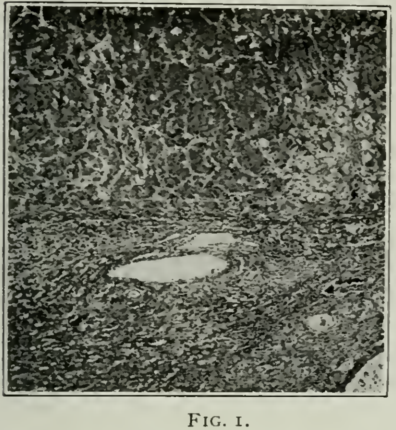


FIG. 1.

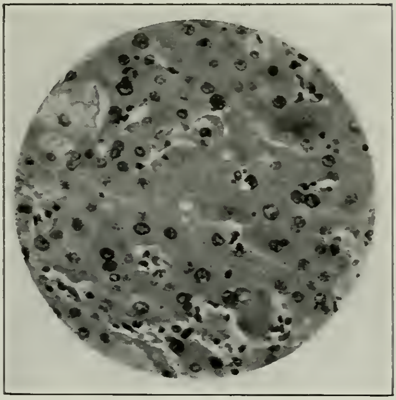


FIG. 2.

FIG. 1. Hepatoma, separated from normal liver by zone of round-cell infiltration. Low power.

FIG. 2. Hepatoma. High power.

Microscopic examination of the excised nodule showed it to be a typical Rokitansky liver-cell adenoma or so-called hepatoma (Figs. 1 and 2). The cells, though they resemble liver cells are much larger, take a deeper stain, and are not arranged in the same orderly fashion. They possess a large amount of granular, acidophilic protoplasm and small vesicular nuclei, which generally show a single nucleolus. There is some variation in the size of the cells and nuclei and large cells with a single, large, or several small nuclei are occasionally observed. Mitosis is not active. In the center of the tumor nodule there is some fatty degeneration of the cells. The tumor is split into larger and smaller, irregular lobules by bands of fibrous tissue, but there is no tendency to form acini, the cords and islands of tumor cells being supported merely by thin-walled capillaries. The growth is partially surrounded by a fibrous capsule, though in one area tumor cells have broken through the capsule and are irregularly distributed among the surrounding atrophic liver cells, and in other places the tumor tissue is separated from the adjacent liver tissue by a zone of round-cell infiltration.

Histologically the tumor seemed to be benign. A Wassermann taken after operation showed 4 plus with natural amboceptor and negative after anti-sheep amboceptor had been added. This suggested the possibility of a syphilitic infection and it was hoped that perhaps the liver condition might be explained on that basis. Sternberg[2] has called attention to the fact that in

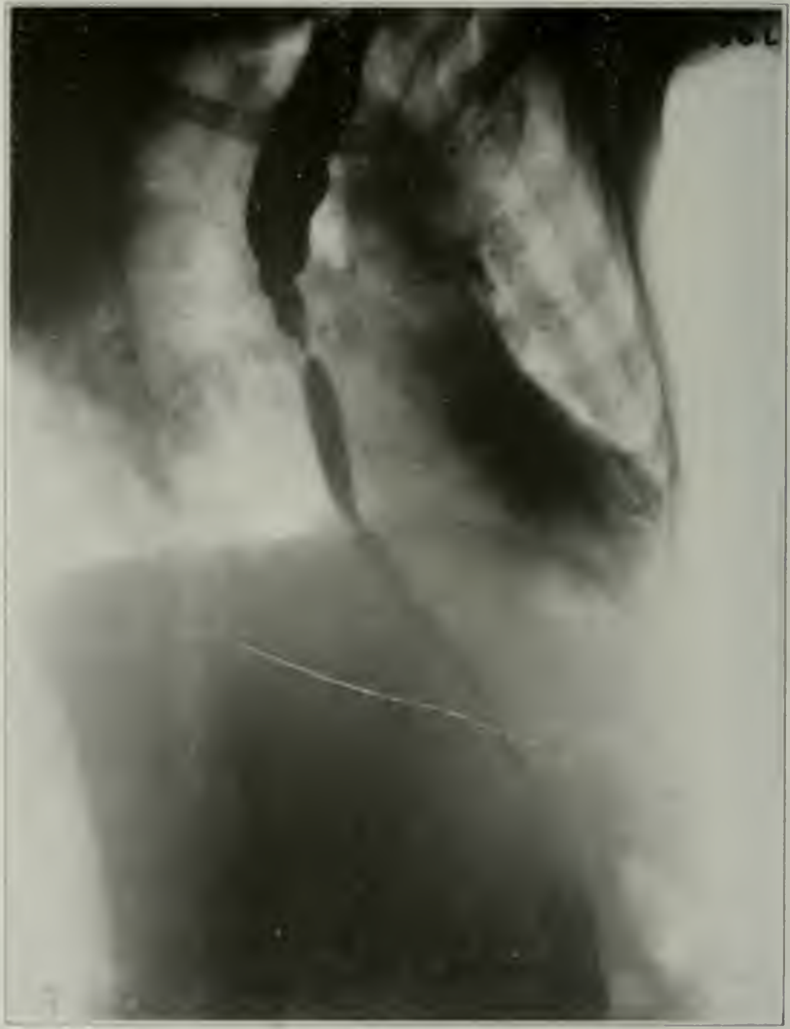


Fig. 3. Radiograph of esophagus, showing obstruction in lower third.

certain forms of nodular adenomatous hyperplasia of the liver, compensatory to various destructive processes, great difficulty occurs in differentiating these lesions from the true adenomata. On this theory and in the hope of arresting further liver destruction, a course of anti-syphilitic treatment was begun, but soon abandoned, as it was not well tolerated and showed no results, and as a subsequent Wassermann was negative.

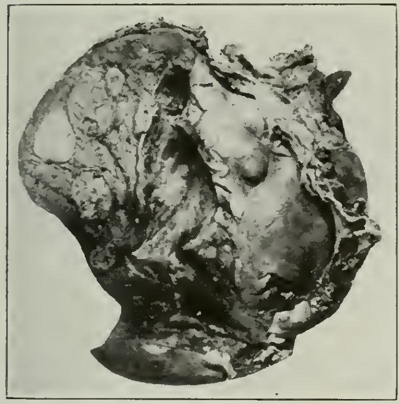


FIG. 4.

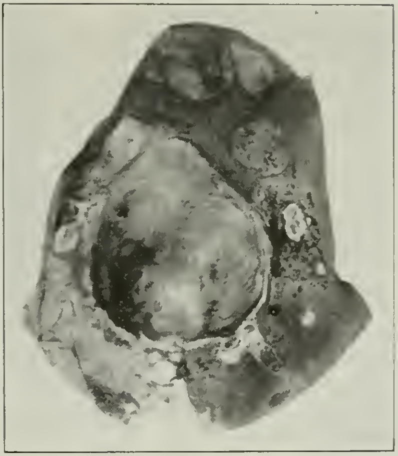


FIG. 5.

FIG. 4. Gross appearance of hepatomata of liver.
FIG. 5. Gross appearance of hepatomata of liver, with large necrotic tumor in center of organ.

About two weeks after operation the patient began to complain of dysphagia. X-ray examination of the esophagus (Fig. 3) and esophagoscopy showed a marked obstruction, undoubtedly organic in character, in the lower third of the esophagus. Whether the lesion was intra- or extra-esophageal could not be positively established, but on November 27, 1920, a gastrostomy was performed. On December 16, 1920, the patient died from asthenia.

Postmortem examination showed the following important changes:

The liver is somewhat enlarged but very much distorted by numerous nodules which project from beneath the capsule (Fig. 4). These nodules are circumscribed, of pinkish-white color, and granular surface. They vary in size from 0.5 to 12 cm. in diameter. About the center of the organ is a large tumor of this type which has undergone complete necrosis, the necrotic material being bile green (Fig. 5). Vascular emboli are demonstrable in the gross, projecting from veins which are visible on the inner wall of the cyst left by the necrosis of the tumor tissue.

Scattered throughout the lungs are pinkish-white, circumscribed nodules ranging in size from a pin-head to 2 cm. in diameter.

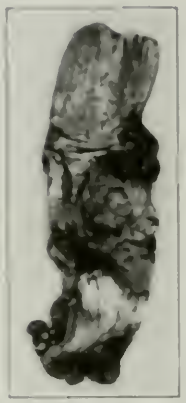


FIG. 6

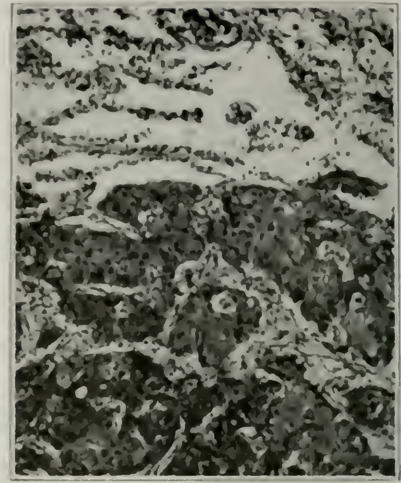


FIG. 7

FIG. 6. Gross appearance of squamous-cell epithelioma of esophagus.
FIG. 7. Metastases in lung from hepatoma.

The esophagus shows, approximately 16 cm. from the cardia, a stenosing ulcer, involving over three-quarters of the circumference of the tube and measuring 3 x 2.5 cm. in its greatest diameters (Fig. 6). The base of this ulcer is friable, granular, and its edges are not indurated.

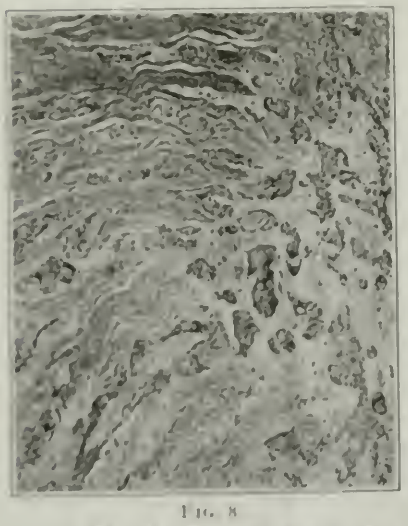


FIG. 8

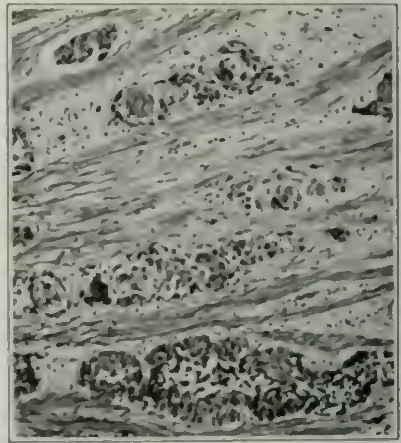


FIG. 9

FIG. 8. Squamous-cell epithelioma of esophagus. Low power.
FIG. 9. Squamous-cell epithelioma of esophagus, showing pearl formation. High power.

The microscopic examination of the tumors of the liver (Figs. 1 and 2) and of the nodules in the lung (Fig. 7) shows them to be of the same character as the nodule originally excised for diagnosis at the first operation—namely, liver-cell adenoma or hepatoma, primary in the liver and metastatic in the lung. In the liver tumors blood vessel emboli are demonstrable and there is extensive degeneration and necrosis in many of the neoplastic areas. Elsewhere the liver shows a mild degree of cirrhosis of the intralobular type.

The ulceration in the esophagus shows a necrotic surface beneath which are islands and columns of epithelial cells of the stratified, squamous variety in which intercellular bridges and occasional pearl formation are demonstrable (Figs. 8 and 9). These neoplastic cells have invaded the muscle to a considerable depth. The lesion has all the characteristics of a typical squamous-cell epithelioma of the esophagus.

In conclusion, I wish to acknowledge my indebtedness to Drs. G. L. Rohdenburg and F. D. Bullock for their help in the pathological study.

References

1. Harbitz: Ueber das gleichzeitige Auftreten mehrerer selbständig wachsender ("multipler") Geschwülste, *Beitr. z. path. Anat. u. z. allg. Path.*, 1916, lxii, 503.
2. Sternberg: Aschoff's Pathologische Anatomie, 1913, Ed. 3, II, 894 and 901.

Discussion:

Dr. Rohdenburg: A number of years ago I presented a series of tumors primary in the liver, some of the gall bladder, and others of the liver cell type, and I was particularly anxious to have Dr. Stetten present this case here to-night, because at that time Dr. Ewing said one of my cases was unique in that there were metastases in the lymph nodes, and that he had never seen metastasis in a carcinoma of the liver of the hepatoma type. This particular case emphasizes that metastases do occur much more beautifully than the cases I showed.

Dr. Symmers: Was there evidence of bile staining?

Dr. Stetten: The necrotic central tumor was bile stained.

Dr. Wood: This is an extraordinarily interesting case because it illustrates very well the question of malignancy of tumors of this type. The primary growth in the liver does not differ from the adenomata seen in cases of cirrhosis, and the carcinoma in the lung is also very close to the type we find similarly associated. The tumor shows how little morphology has to do in the determination of the malignancy of some of these adenomatous neoplasms. This is well known in connection with the thyroid tumors which may metastasize and form nodules of tissue very closely resembling normal thyroid. It is impossible to believe that without metastases such tumors are malignant. There was a little bile in some of the metastases in the lung. This is very interesting more from the general point of view of the nature and the biological qualities of the cells. Here is a liver tumor which is malignant because it has metastasized, but the cells of which are so slightly altered from the normal liver cells that they are still able to perform a considerable function, and it is difficult to consider that their chemistry and their general biological nature are very different from the normal liver cell. I think we are all coming to the realization that the cells of a carcinoma and the cells of the original tissue from which the tumor is derived are only slightly different. At the Crocker Laboratory we are doing experiments all the time to attempt to find out some differential point between the carcinoma cell and its homologous tissue, and the more we work the less difference we find. A long series of experiments have been carried out on the question of the hydrogen ion reaction of tumor cells and the homologous tissues, and we do not find any differences. It is well known that there are no general serum reactions following the growth of a tumor. The old belief of the production of cachexia by a tumor toxin is now practically abandoned. We see animals carrying tumors corresponding to one or two feet in diameter in the human being. Such animals are not in the slightest degree cachectic, and show no evidence of ill health except that they have a large lump. Pathologists are being forced gradually to the conclusion that the difference between the carcinoma cells and the homologous normal cell of the same growth rate is most minute and escapes all analysis.

Dr. Larkin: I think the simultaneous occurrence of different types of tumor in the same individual is not at all uncommon. The occurrence of simultaneous tumors of different types was pointed out by Virchow, and it has been my privilege to study a number of such tumors. From the description which Dr. Stetten gives, especially as regards the liver tumor, it would seem to me that that tumor is unusual, and is really a hepatoma.

The simultaneous occurrence of the epithelioma of the esophagus is rather unusual, and it is worthy of great attention. It may be interesting to know that only this afternoon we had an individual brought to the hospital with a very large tumor and there was a section made from the liver on which a diagnosis of primary carcinoma of the liver was made, probably an adenocarcinoma of the gall bladder ducts. There was nothing found in the abdominal cavity except this very large tumor. The stomach seemed to be normal.

Dr. Stetten: I want to say a word about the question of cirrhosis. I was much more interested in this case from the surgical and therapeutic standpoint than from the pathological, and when we first excised the nodule and the report was received, I tried to persuade Dr. Rohdenburg that maybe we were dealing with one of those adenomatous nodules found in the hyperplasias, compensatory to destruction of the liver, and I even gave him some references to an article by Sternberg in Aschoff's Pathology, in which he distinctly says it is often impossible to differentiate these lesions from true adenomata. Dr. Rohdenburg was willing to admit that perhaps this was so. When we obtained the 4 plus Wassermann with the natural amboceptor we gladly accepted syphilis as the cause of the trouble, and hoped that we were going to cure the man by giving him anti-specific treatment. After the first operation he actually improved somewhat and appeared to be getting better. I was interested in presenting the case, not so much on account of the nature of the liver tumor, but because of the simultaneous occurrence of the two different types of malignant tumor, suggesting that the patient exhibited a distinct tumor diathesis, upon which Virchow laid so much stress years ago.

DEMONSTRATION OF LEPTOSPIRA ICTEROIDES, WITH NOTES ON THE RESULTS OF PROPHYLAXIS AND SERUM TREATMENT OF YELLOW FEVER

HIDEYO NOGUCHI, M.D.

(From the Laboratories of the Rockefeller Institute for Medical Research)

Leptospira icteroides was first isolated in 1918 from cases of yellow fever in Guayaquil by the speaker; later the organism was obtained from yellow-fever cases in Mérida, Yucatan (Noguchi and Kligler, 1919) and in northern Peru (Noguchi and Kligler, 1920). The finding was also confirmed in Mexico by Dr. Perez Grovas, in Vera Cruz in 1920, and by Le Blanc of the Rockefeller Institute in the same city in 1921. Gastiaburú, of the Instituto de Higiene of Lima, transmitted yellow fever to guinea pigs from cases occurring during an epidemic in Piura, Peru, in 1919.

The killed cultures of *Leptospira icteroides* were first used for protective inoculation against yellow fever in Guayaquil in 1918, where 427 vaccinations were carried out. The results were so encouraging (the morbidity rate among vaccinated and unvaccinated during the same period being 11 and 110 per thousand respectively) that a vaccine several hundred times stronger has been made in large quantities and employed in Mexico and various Central and South American countries, the total number of non-immune persons reported vaccinated being about eight thousand. The development of protection, as in the case of all vaccines of this kind, requires about ten days for completion, and persons exposed to yellow fever just before vaccination or immediately afterwards are not protected by vaccination. Excluding such instances, however, there has been no case of yellow fever among the eight thousand vaccinated in the various localities, while among unvaccinated persons during the same period and in the same areas there have been about seven hundred cases of the disease.

The use of vaccine furnishes a rapid method of elimination of non-immune persons from areas where yellow fever is epidemic. By the application of sanitary measures to eliminate the mosquito carrier and vaccination in the meantime to cut off the supply of non-immune material from the infected mosquitos, a threatening epidemic of yellow fever in Guatemala and Salvador in 1920 is reported to have been checked within one month from the appearance of the first cases, that is, before a second set of cases had developed. The value of vaccination as an emergency measure does not, however, minimize the importance of the anti-mosquito operations, since both factors—the non-immune human being and the infected mosquito—must be eliminated in order to eradicate yellow fever.

Leptospira icteroides in the liver of the guinea pig. Guayaquil strain. × 1,000.

A therapeutic serum is also available for treatment of yellow fever. It has already been employed in 170 cases, and persons treated before the third day of illness have almost invariably recovered, the exceptions being those cases in which the quantity of serum used was too small to have any effect. By the fourth day of illness the injuries to organs are so great as to be irreparable in severe cases of yellow fever. The usual mortality in yellow fever, fifty to sixty per cent., has been reduced to 13.6 per cent. by the use of the serum.

The records of vaccination and serum treatment presented here comprise the work of a number of observers. The initial vaccination experiments in Ecuador were carried out with the cooperation of Dr. Pareja and the Direccion de Sanidad of Guayaquil; the statistics from Central America cover the work of Drs. Lyster, Bailey, and Vaughn; for the records of Mexican cases I am indebted to the Consejo Superior de Salubridad (Drs. Vasconcelos and Casasús), to the Junta de la Sanidad de Yucatan (Dr. Hernandez), and to Dr. Le Blanc; the Tuxpan statistics were furnished by Drs. Lynn and Guadarrama; the work in Peru was done with the cooperation and assistance of Dr. Kligler and Peruvian health authorities.

A COMPLEMENT FIXATION TEST OF VALUE IN THE CLINICAL DIAGNOSIS OF TOXIC THYROID STATES

WILLIAM N. BERKELEY, M.D.

A scientifically exact method for the clinical diagnosis of plus, minus, and toxic thyroid states would be a great boon to clinical medicine; and the problem is not insoluble, but the solutions heretofore suggested are not entirely satisfactory.

E. C. Kendall,[1] among others, has proposed the basal metabolism as a guide to the existence of hypo- and hyper-thyroid conditions. But apart from the expense and complicated procedure of this method is the objection that no one yet knows how many other clinical conditions may temporarily influence the basal metabolism in both plus and minus directions. The advocates of this method, as it makes no provision for thyroid toxins, dispose of the matter by denying the existence of such bodies.

E. Goetsch[2] has suggested the severity of the patient's reaction to a measured hypodermic dose of adrenalin as a measure of his thyroid activity. I can not learn that this test has proved generally confirmatory of evident clinical signs. One medical friend of mine with large clinical experience thinks it a dangerous method, causing sometimes a violent and alarming reaction. M. S. Woodbury,[3] in a study of some fifty recent cases of thyroid disease at Clifton Springs, N. Y., concludes that the adrenalin test is an indicator of "general sympathetic hypersensitiveness" which may or may not be of thyroid origin. Further reports[5], [6], [7], from other observers are unfavorable.

It was my idea at one time that if the thyroid secretion appears in the blood in a protein form (it seems generally agreed that it is in protein form in the thyroid gland), it might be picked up by a complement fixation test and titrated. In order to try out this supposition the following experiment was repeated a number of times: A healthy young sheep was immunized by successive injections of a saline suspension of thyroids from freshly killed dogs. Using the injection as antigen, a pronounced and abundant antibody could be demonstrated in the sheep serum in the course of a few injections. But not the slightest binding could ever be observed with normal dog serum as antigen. This seems to prove either that the thyroid secretion is not present in the serum at all in protein form, or that, if so, it is in too minute amount to be available for a fixation test. As I have not found any mention in the literature of such an experiment as this, it seems worth while to record it even in its present fragmentary form.

Failing in this attempt, my attention was turned to the possibility that when the chemistry of the thyroid gland is materially disturbed, as in exophthalmic goiter, the thyroid toxins (assuming for the time that such bodies exist) might be accessible to study by the same (complement fixation) method.

There is almost no literature on this subject that I have been able to find, except some pioneer work done almost ten years ago by Prof. Marinesco, and his associate, A. Papazolu.[4] The latter of these observers claims to have found antibodies a number of times in the serum of patients suffering from Basedow's disease. He used as antigen aqueous, alcoholic, and ethereal extracts of Basedow goiters, parenchymatous goiters, and normal thyroids. Of his 38 tests 14 showed complete fixation, 12 almost complete fixation, and 12 were negative.

This work, while interesting and suggestive, dates back to the very early days of scientific serology, and seems not to have been very carefully controlled. Moreover, Papazolu used alcoholic and ethereal as well as aqueous extracts of his thyroid antigens, thereby, of course, getting fixation with many luetic subjects.

Using non-lipoidal antigens (for method of preparation and serological technique, see Mr. Koopman's note) derived from various thyroid tumors (about ten in all), it has been impossible to get fixation with the serum of Graves' disease except in the case of a single goiter kindly given us by Dr. John Rogers. This growth Dr. Rogers thought to be a true Graves' tumor. Unfortunately it was all extracted, nothing being left for microscopic examination. Antigens from four normal human thyroids gotten at autopsy under favorable conditions entirely failed to bind.

About this time, through a fortunate combination of circumstances, Mr. Koopman observed that with *normal dog thyroid* random samples of Basedow serum would bind powerfully, and that they would not bind with any other dog organ.

Starting out with this test as a guide—*i.e.*, using dog thyroid as antigen—fixation experiments have been done on more than 195 human serums, of which 44 were under suspicion of positive thyroid dyscrasia.

Of the 44, 18 were clinically undoubted Graves' disease, 2 were probably so, 14 were doubtful, and 10 were probably *not*

Graves'. I have full notes of most of these cases; in all the instances where the blood only was sent (through the courtesy of medical friends kindly interested in the research) the diagnosis was made by a colleague in whom I had unusual confidence. I believe the chances of error in this regard are reasonably remote.

The 18 Graves' cases were all one plus to four plus. The probable cases were positive; 10 of the 14 doubtful cases were positive; the ten "probably not" were all negative.

As to the controls, numbering over 140 patients, all were negative except one. This exception was a young married woman of about thirty years, with a tertiary specific skin lesion on one knee. She was not particularly nervous; her pulse was 96; her eyes and thyroid did not strike one as pathologically prominent. She had a positive Wassermann and a positive thyroid fixation. She was lost before it was possible to make any further investigation of her history and condition. All the other controls—representing nearly all the chronic and many of the common acute diseases (non-infectious)—were, as already noted, negative. About 20 were old fibrocystic goiters. About 20 more were puberty enlargements. Serum kindly sent us by Dr. George Draper from a borderland case was, he reported, negative to the Goetsch test; we found it two plus positive to the dog thyroid test. Another serum (Dr. Jos. H. Fobes) was positive to the Goetsch test, and also two plus with dog thyroid.

The new test has been repeated hundreds of times and has been checked up with all needful controls. If anyone alleges that the binding is due merely to the chance appearance in human serum now and then of a native amboceptor, then he must also explain why in more than ninety-five per cent. of the cases the native amboceptor appeared in patients with a positive thyroid dyscrasia.

Speaking further for the value of the test is the fact that in several of the positive cases which have improved very much or apparently gotten well in the last eighteen months, the test has varied concomitantly with the clinical improvement, falling from four plus to two plus, and later disappearing entirely. Dr. H. H.

Janeway, of the N. Y. Memorial Hospital, who has recently experimented extensively with radium in these cases, tells me that he considers the test of distinct value in the quantitative adjustment of such treatment to the clinical condition of the patient.

The number of cases so far observed is too small to make the suggestion more than tentative, but with this reservation I venture to hope that the new test may be found of value in several directions:

1. In the clinical diagnosis of a great many cases which are now very perplexing—early cases, late cases, borderland cases, anomalous cardiac neuroses, and thyroid tumors without definite signs of thyroid poisoning, such as unusual menstrual swellings, post-puberty enlargements, and fibrocystic goiters in the early stages. Such a test would help to differentiate exophthalmos due to other causes than Graves' disease, and would eliminate many cases of severe tobacco poisoning due to cigarettes, where the symptoms and signs (as recently noted in army soldiers and recruits) have been such as to deceive the very elect.

2. The test would aid in the adjustment of therapeutic measures to the immediate condition of the patient.

3. The test is simple, inexpensive, and absolutely harmless.

4. And finally it might throw considerable light upon the etiology of cellular tumors in general.

Subject to later modification the view may be suggested that spontaneous recovery in exophthalmic goiter is due directly to the formation of these corrective antibodies in the patient's own system; and that rest, careful feeding, and relief from anxiety contribute to the cure merely by aiding the patient's normal immunity-mechanism.

Bibliography

1. Kendall, E. C.: *Journal A. M. A.*, 1918, lxxi, p. 871, and *passim* in recent medical literature.
2. Goetsch, E.: *N. Y. State Journal of Medicine*, 1918, xviii, p. 259.
3. Woodbury, M. S.: *Journal A. M. A.*, 1920, lxxiv, 997.
4. Papazolu, A.: *Séances et Mémoires de la Soc. de Biol.*, 1911, lxxi, 671.
5. Sandiford, Irene: *Am. Jour. Physiol.*, 1920, li, 407.
6. Marine, D., and Lenhart, C. H.: *Am. Jour. Physiol.*, 1920, liv, 248.
7. Mayo, C. H.: *Journal A. M. A.*, 1921, lxxvii, 353.

TECHNIQUE OF COMPLEMENT FIXATION REACTION IN BASEDOW'S DISEASE

JOHN KOOPMAN

The blood of some patients who show symptoms of Basedow's disease binds complement in the presence of an antigen made from normal thyroid glands.

The reaction may be due to a specific thyroid substance which combines with an antibody in the blood of the patient.

The best method of preparing the antigen which we have been able to find is as follows: The glands are obtained under aseptic precautions as soon as possible after the dogs have been killed. Each gland is trimmed carefully and minced finely with sterile scissors. The whole mass is then ground in a mortar with a measured quantity of washed and sterilized sand and of dry sodium chloride. The amount of sand is of no importance, but the salt should be added in the proportion of 1/10 gram to each gram of gland used; a few drops of 2 per cent. aqueous solution of tricresol are added for each ten grams of thyroid. This mixture is bottled and laid away in the ice-box. For use it is made up with distilled water, using 10 c.c. of water to one gram of the original amount of gland. The sand and solid matter are removed with the aid of a centrifuge.

It is best to use the mixed glands of five or six dogs. As at present prepared, the extract contains much extraneous matter which takes no part in the reaction; if some method of securing the antigenic substance free from all foreign matter could be devised, the specificity would be enhanced. As far as we have gone, we know that the antigen slowly deteriorates even when kept under the best conditions, and after about three weeks it is necessary to obtain a new supply. Drying instantly spoils its antigenic properties and it does not withstand heating to 50° C. for fifteen minutes.

The test is set up in the form of a titration, using a constant amount of serum which is not more than one quarter of the least amount which is anticomplementary. The antigen is used in varied amounts, beginning with an excess and ending with the least amount which can be expected to give fixation. The exact amounts used will depend upon the total volume of the test the worker is accustomed to using. At the same time an antigen control is made with the same quantities of antigen as are put in the test. This procedure will obviate the necessity of putting in a separate titration of the antigen before the test itself is made. The result is indicated by the difference between the quantity of antigen which is anticomplementary of itself and the quantity which binds complement in the presence of serum. A negative serum with the antigen will often bind less complement than the antigen alone.

A serum is considered positive when it binds complement in the presence of one half or less than one half of the anticomplementary dose of antigen, and the smaller the amount of antigen necessary for complete fixation the stronger is the reaction. Fixation is carried out for from four to six hours in the ice-box. At the present time the range is short, but with improved methods of preparing the antigen it is hoped the range will become greater.

Besides the tests on human glands and human tumors (*i.e.,* thyroid tumors), as above mentioned, we have tried the glands of some other animals, namely, guinea pig, bullock and pig, and we find that guinea-pig glands give results comparable with the dog antigen.

Much more work also remains to be done on fixation results with extracts of true exophthalmic goiters. These are now very hard to get in New York operating rooms, as surgical removal of them has gone out of fashion; and we have not been able to devise any way of keeping them in fit condition for antigen formation for more than two or three weeks.

Discussion:

DR. NOGUCHI: Was the fixation complete?
MR. KOOPMAN: Yes.
DR. NOGUCHI: How much serum was used?

MR. KOOPMAN: Not more than about one-fifth or one-sixth of the anticomplementary amount.

DR. NOGUCHI: In absolute quantities, what would that be?

MR. KOOPMAN: Using 0.10 c.c. of 10 per cent. complement that would be about 5/1000 c.c.

DR. NOGUCHI: Do you find many human serums anticomplementary?

MR. KOOPMAN: With ordinary cases perhaps one or two per cent. of the sera will be anticomplementary; and of fresh sera not more than one-tenth of one per cent.

PROBABLE SYPHILITIC INTERSTITIAL PNEUMONIA IN AN ADULT

ROLFE FLOYD, M.D.

Syphilis of the lung took a definite place in medical literature about one hundred years ago, and from that day to this it has always been a difficult and often an uncertain diagnosis for the pathologist. Clinicians, on the other hand, have not hesitated from time to time to make the diagnosis easily and often, especially about 1880, when syphilitic phthisis was a frequent complaint, curable at certain European Spas, and again very recently, when X-ray lung shadows which diminish after antisyphilitic treatment, particularly if associated with a positive Wassermann, are considered, with altogether unwarranted assurance, to be a sufficient basis for the diagnosis. Rössle, a present German writer, considers syphilis of the lung as frequent as syphilis of the liver, and Carrera,[1] working in Warthin's laboratory, considers its incidence similar to that of syphilis in the other internal organs. The average incidence, however, reported by competent pathologists of wide experience is about one or two cases per thousand autopsies.

The discovery of the *spirochæta pallida* has failed to throw the expected light on pulmonary syphilis, because it has proved practically impossible to demonstrate this organism in the lungs of adults; Koch and Schmorl[2] and Warthin being the only ones to find it so far.

It is thus a peculiar fact that a generation after the discovery of the tubercle bacillus, and half a generation since the discovery of the causative agent of syphilis, the diagnosis of syphilis of the lung still rests primarily on pathological anatomy.

Gummata of the lung, both in infants and adults, are accepted as definitely luetic, though sometimes difficult to distinguish from tubercular lesions. Again the so-called white pneumonia of infants is considered syphilitic by practically all observers.

It is concerning interstitial pneumonias of adults that it is the hardest to say whether they are syphilitic or not, for this condition results from many causes besides lues; thus persistent broncho-pneumonia, lobar pneumonia followed by fibrous organization, certain forms of pulmonary tuberculosis, invasion of the lung by inflammatory connective tissue from the pleura, the peribronchitic indurations that occur with prolonged irritation by dust, some extreme types of chronic congestion and unusual changes produced by foreign substances, as in broncho-esophageal fistula, may all result in extensive interstitial changes in the lung parenchyma.

Accumulating experience, however, has gradually established the following as the characters on which an adult interstitial pneumonia is to be judged syphilitic:

1. The presence of tertiary syphilitic lesions in other organs. This is a most important criterion, as well as one of the first to be recognized. In the absence of such a lesion extreme conservatism must be exercised in considering an adult interstitial pneumonia syphilitic.

2. Gross characters of syphilitic interstitial pneumonia, which are: (*a*) location in the lower lobes; (*b*) white fibrous foci, often multiple and more or less confluent with large and small radiating fibrous bands which may reach the pleura and cause a coarse puckering of it through contraction; or similar bands arising as direct extensions of the inflammatory connective tissue wall of ulcerated and stenosed stem bronchi; (*c*) the absence of necrosis and of calcification.

3. Microscopic characters, which are more diagnostic than the gross and consist of: (*a*) an extensive inflammatory over-

growth of the pulmonary connective tissue framework, the new tissue at first full of fibroblasts and thin-walled blood vessels, later becoming more densely fibrous; (*b*) round cells scattered through this tissue especially in foci and most typical when in perivascular concentrations. The alveoli, as in interstitial pneumonia of other types, are often reduced to small spaces lined by cuboidal epithelium. Sclerosis of the arteries is frequent. Giant cells are much less frequent than in tuberculosis, while miliary gummata and necrosis are not described in this form. Masses of smooth muscle mixed in with the new areolar connective tissue have been noted by Tanaka.[3] The amount of anthracosis and of elastic fiber destruction are still matters of dispute.

A complete bibliography and an extensive review of the literature is given by Carrera,[1] to whose paper the reader wishing such information is referred.

It is evident that no diagnosis can be considered beyond question on such relative grounds, and that its probability will depend on the number and importance of these features present in each particular case. It is with full realization of this uncertainty that the following case is submitted for consideration.

A woman thirty-four years old was brought into Bellevue Hospital with a general septic peritonitis of which she died three days later. Signs of consolidation and pleurisy were found over the right lower lobe, and it was supposed she had a lobar pneumonia (especially as an exploratory puncture yielded no fluid). There was an artificial anus in the left iliac fossa which she said had been made at the New York Hospital three years previously to relieve an acute obstruction. She had been told at that time that she had a tumor of the rectum, and examination at Bellevue revealed a tight stenosis.

A hæmolyzing streptococcus was found in the blood during life and also cultivated from the spleen after death.

There is no mention of a Wassermann reaction.

The autopsy, done seven hours after death, showed principally: general septic peritonitis and septicæmia; interstitial pneumonia of the right lower lobe with acute fibrinous pleurisy over it; syphilitic stenosis of the rectum, and a large fatty liver.

The right lower lobe contained but little air; it was congested and contained numerous white fibrous foci, more or less confluent in places, from 0.5 to 1 cm. in diameter, from which white strands radiated, some of them reaching the pleural surface. These zones were most numerous below and behind (Fig. 1). There was no fibrosis near the root nor any lesion of the trachea and large bronchi except recent congestion. The overlying pleura showed an exudate of recent fibrin but was not puckered, or thickened or adherent.

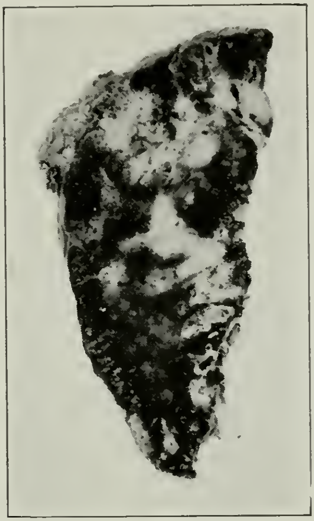


FIG. 1. A small piece of the right lower lobe showing the white, fibrous zones. Natural size.

There was an annular ulcer of the rectum, starting at the anus, extending three inches upwards, and limited by a worm-eaten edge above. Massive thickening of the rectal wall beneath the ulcer caused stenosis almost to the point of occlusion.

Under the microscope the white zones in the lung consist of fibrillated and areolar connective tissue with many elongated nuclei and also many of dumb-bell and other irregular forms. The tissue is well supplied with thin-walled blood vessels (Fig. 2).

Round cells occur all through it, often in distinct foci which frequently show the remnants of a compressed bronchiole or alveolus in the center (Fig. 3). Perivascular round-cell concentrations also occur, but they are not as large or distinct as those found independent of vessels.

Pus cells lie scattered through the connective tissue, probably incidental to the general sepsis.

Compressed alveoli, oval or slit-shaped and lined by cuboidal epithelium, are fairly numerous; if a lumen persists it often contains pus cells (Fig. 3).

Bronchial remnants with higher epithelium huddled together so as to obliterate the lumen also occur; remnants of smooth muscle may be seen about them.

Arteries do not penetrate far into the new tissue. Those on the periphery often are surrounded by round cells, as already described. They show little or no sclerosis.

The lung tissue between the new connective tissue zones is airless, collapsed and congested, the collapse due either to pressure by the expanding connective tissue or to atelectasis resulting from occlusion of bronchioles.

Van Gieson's stain brings out the interstitial connective tissue zones clearly and their rather abrupt transition to areas of collapsed lung.

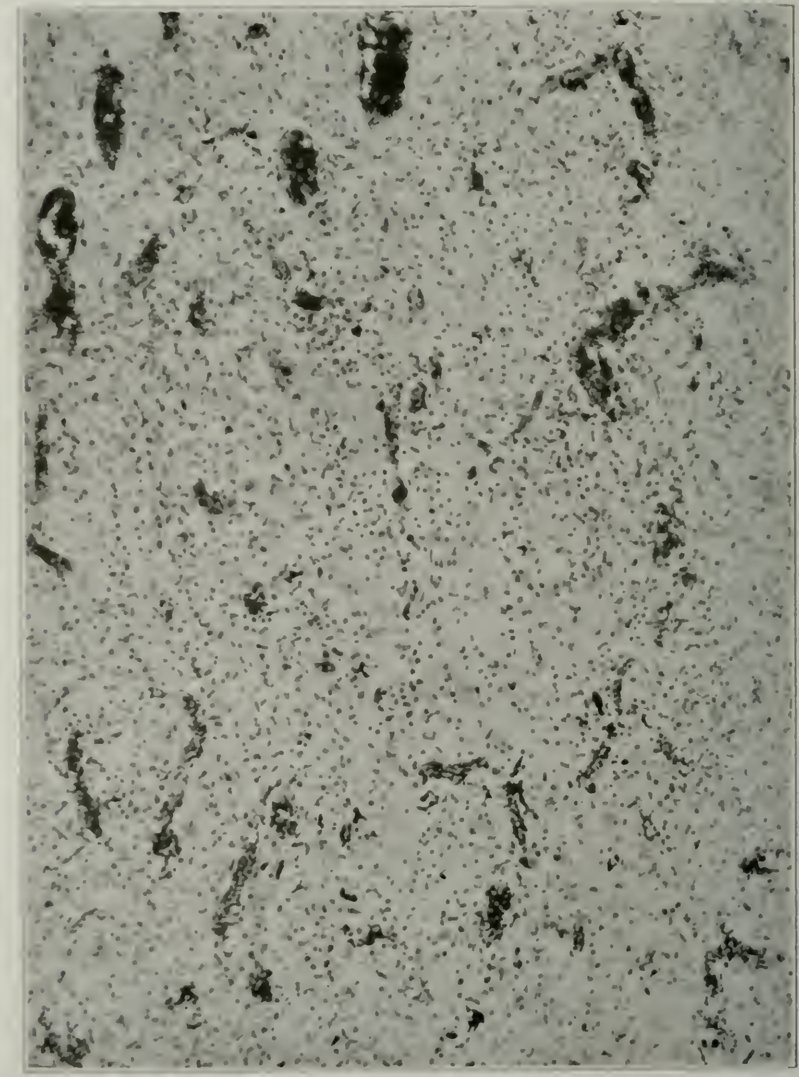


FIG. 2. Fibrillated vascular connective tissue from one of the fibrous zones.

Sections stained by Warthin and Starry's recent improved method showed no spirochætes.

The rectal wall shows, in its deeper layers, sclerosis of the larger vessels and an infiltration of round cells in the perivascular spaces of both large and small vessels. The muscle bundles are separated by fibrous

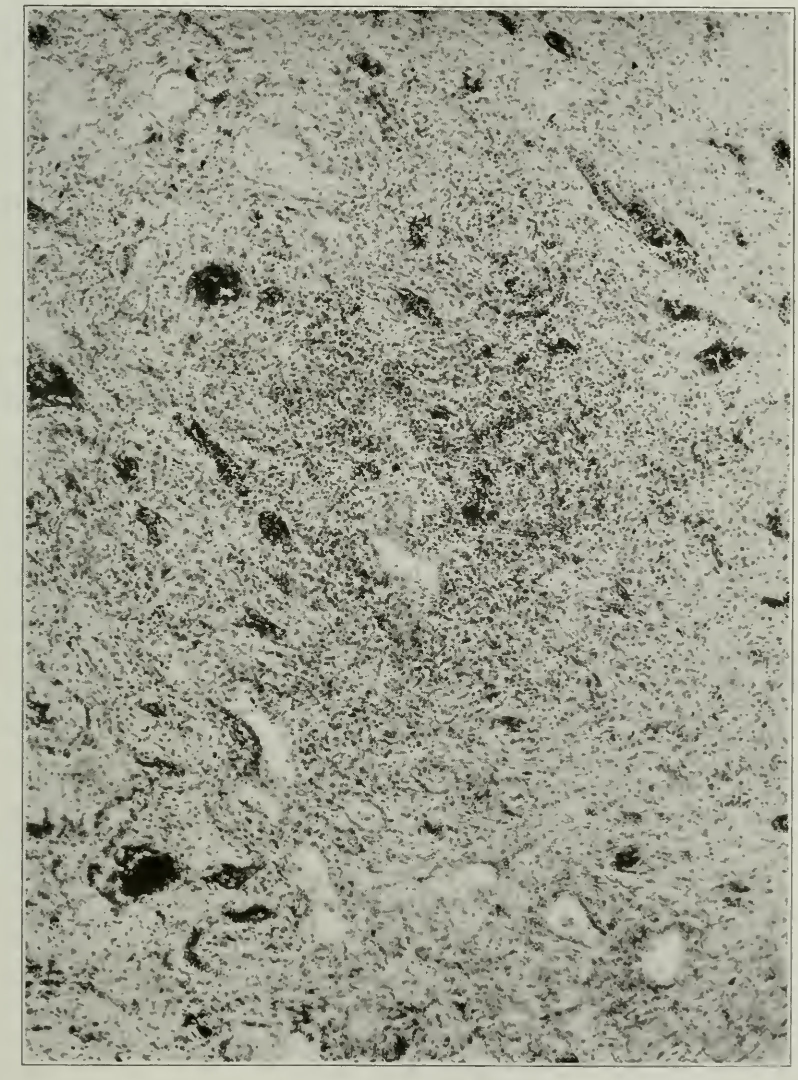


Fig. 3. A round-cell focus in the new fibrous tissue, centering about a compressed alveolus lined with low cuboidal epithelium. Other similar alveoli may be seen beyond the margins of the round-cell focus.

strands which are also densely infiltrated with round cells. The more superficial layers are enormously thickened and changed into firm fibrillated tissue, very densely infiltrated with round cells, continuous with a surface layer of granulation tissue, entirely devoid of all traces of mucosa.

The liver shows a decided amount of fat in the hepatic cells and a distinct infiltration of round cells along the portal canals with a tendency to form foci. There are also pus cells along the portal canals and through the sinusoids.

The reasons for thinking this interstitial pneumonia syphilitic are: (1) the presence of typical syphilitic stenosis of the rectum and probable syphilis of the liver in the same body; (2) the situation of the interstitial pneumonia in the lower lobe, the presence of multiple white foci with radiating bands, without necrosis or calcification; (3) the enormous growth of vascular interstitial connective tissue containing many round cells in foci and perivascular concentrations.

References

1. Carrera: *Am. Jour. Syphilis*, 1920, iv, 1.
2. Koch and Schmorl: *Verhandl. d. deutsch. path. Gesellsch.*, 1907, 2 Tag.
3. Tanaka: *Virchow's Arch. f. path. Anat.*, 1912, ccviii, 429.

Discussion:

Dr. Moschcowitz: Dr. Floyd's remarks have offered me considerable consolation. I have a specimen in my possession which I believe is syphilis of the lung, but I hesitated to present it here because I never could demonstrate the spirochete. This lung was found in a patient in whom syphilitic lesions were found elsewhere in the body. She had a syphilitic pancreatitis and a syphilitic perihepatitis. The lower lobe of the lung was completely solid with interstitial pneumonia. I am also fully in accord with what Dr. Floyd said about the clinical diagnosis of syphilis of the lung. That diagnosis is very frequently made. If a patient has clinical symptoms of a pulmonary lesion, and a positive Wassermann is found and an X-ray shadow is present which disappears after salvarsan treatment, the diagnosis is put down as "syphilis of the lung." A close analogy is that of syphilis of the stomach, which is also a frequently made diagnosis. Cases are reported with gastric symptoms and a positive Wassermann reaction, and if under anti syphilitic treatment the patient gets well, the diagnosis is made of syphilis of the stomach. I think the majority of us would say that syphilis of the stomach is probably one of the rarest lesions found on autopsy.

MALIGNANT TUMORS OF THE LUNG

A. V. ST. GEORGE, M.D.

(From the Pathological Laboratories, Bellevue Hospital, New York)

Primary neoplasms of the lung and associated structures have always been considered a great rarity. Isaac Adler, in 1912, called attention to an apparent increase in primary lung tumors and in the past year or two case reports have been noted more often in medical literature. The increase in the number of cases at Bellevue Hospital seems to bear out Adler's observation.

In Bellevue Hospital, during a period of ten years ending July, 1917, there were three primary lung neoplasms autopsied; from July, 1917, to July, 1919, there were two patients with new growths of the lung coming to autopsy. On the other hand, during a period of twenty months from July, 1919, there were autopsied one case of primary sarcoma of the lung, four cases of primary bronchial growths, one adenocarcinoma of the lung, and one adenocarcinoma of the lung arising from the smaller bronchioles. These seven cases have been made the subject of a paper to be published and are, therefore, merely abstracted here.

Case 1. A case of primary lung sarcoma, presented before this society in March, 1920 (published in the *Proceedings of the New York Pathological Society,* N. S., vol. 20, Nos. 1–5, January–May, 1920), and recorded as an alveolar lung sarcoma.

Case 2. The patient was a man forty-nine years of age, married, colored, a janitor by occupation, who was admitted to Bellevue Hospital on January 30, 1920, and died February 11, 1920. The onset of his illness occurred four weeks previous to admission, characterized by severe pain in the upper right part of the chest, in the infraclavicular region, of short duration but recurring at frequent intervals; the patient also suffered from severe dyspnœa for three weeks. The family history was irrelevant.

Physical Examination: The right eye was absent (removed seven years ago because of trauma); the left eye showed arcus senilis and the pupils reacted sluggishly to light. There was no marked asymmetry of the chest and no expansion on the right side. Dullness was present over the entire right lobe; there were no breath sounds and vocal fremitus was diminished. The left lung was resonant, the breath sounds normal, and there were a few sibilant râles at the base posteriorly. The apex of the heart was palpable in the fifth space, 17 cm to the left, there was no enlargement at the base. A long, soft systolic murmur was heard at the apex; the pulse was of poor quality. There were a few old scars present over the tibiæ; knee jerks were not obtained. Thoracentesis showed bloody pleural fluid (not examined microscopically); the urine was normal and the sputum negative for tubercle bacilli; Wassermann reaction was negative. X-ray showed an effusion into the right pleural cavity. The temperature varied between 98.8 and 100° F.; respirations 24 to 32; pulse 80 to 120.

Diagnosis Chronic endocarditis; myocardial insufficiency with decompensation.

Autopsy (abstract of protocol): The left lung was easily removed and was voluminous. The pleura was glistening and free from adhesions and exudate. The lung pitted on pressure and was cottony to the touch. It cut with difficulty and the cut surface was dry. The right lung was removed with difficulty due to fibrous adhesions which were especially firm posteriorly. Between the visceral and parietal layers there were about 200 c.c. of bloody fluid and partly clotted exudate, which showed a network of fine fibrin. The pleura was enormously thickened, dense and white. The lung was large, greatly increased in weight, solid and non-crepitant throughout. On section, the upper lobe contained a large, irregularly shaped tumor, which presented a variegated appearance, and was yellow, reddish-yellow and gray in color, extremely soft and friable. It bulged from the cut surface. The tumor occupied almost the entire upper lobe, there being only an area of about 1 to 2 cm. of lung tissue surrounding the tumor. This tissue was solid, non-crepitant and, on section, gray and rough, as was also that of the lower lobe. The alveoli on pressure exuded quantities of thick, cream-colored fluid. The bronchi were congested, but showed no other naked eye changes. The peribronchial lymph nodes were enlarged and, on section, showed a white friable tissue, probably metastatic tumor tissue.

Anatomical Diagnosis: Right lung—hemothorax; thickened pleura; fibrinous pleuritis; primary carcinoma of upper lobe; lobular pneumonia of lower lobe. Left lung—emphysema.

Microscopic Examination: Microscopically, the tumor in the lung showed small epithelial cells, fairly uniform in size, with many mitotic figures, solidly filling most of the lung alveoli; only here and there were there remains of unoccupied lung alveoli. Microscopic diagnosis: Carcinoma, arising from the alveolar epithelium of the lung.

Case 3 The patient was a man sixty-one years of age, Scotch, married, a carpenter by occupation, who was admitted to Bellevue Hospital on April 24, 1920, and died June 27, 1920. He stated that he had had a chronic winter cough for years; malaria twenty years ago; five years ago complete blindness, diplopia; influenza one year ago with sudden onset, pain in chest, fever, and cough for seven weeks. Marital history: wife and five children living, one child died in infancy, cause unknown. Habits: bowels regular, occasionally nocturnal urination is excessive; coffee taken, occasionally alcohol, tobacco; one pound per month. Family history: mother and father dead, latter at ninety years of age; two brothers and one sister alive and well.

In the middle of December the patient began to cough and expectorate and feel tired. This progressed gradually until, at the end of February, he expectorated about one-half ounce of bright red blood. Thereafter he became very weak with pain in chest, and had to give up work; he was unable to stay in bed because of feeling of pressure and cough, and slept sitting up. There were constant knife-like pains in the left chest, exaggerated by cough and deep respiration; also anorexia and marked dyspnœa on exertion.

Physical Examination: The thorax was well developed and there was slight retraction of both clavicular fossæ. The apex beat of the heart was heard in the fifth space; there were no murmurs or thrills; the left border was not definable; pulses equal; arteries sclerotic. The lungs showed limited expansion on the left side; the left lung was flat throughout, no breath sounds or râles. The right lung was resonant; the inspiration exaggerated, and there were fine râles posteriorly during inspiration and large and fine râles anteriorly. Physical examination was otherwise negative. On May 10th, it was noticed that the veins of the upper part of the chest and neck were dilated; there were also marked cyanosis and dyspnœa.

Fluoroscopic examination showed the left side to be dense; there were mottled areas and extension of infiltration on the right side; the surface of the lung was extremely hard and nodular, and suggested a new growth. X-ray diagnosis: New growth.

The urine was negative; blood count showed white blood cells 13,000; differential count: polymorphonuclears 78 per cent., transitionals 11 per cent., eosinophiles 1 per cent., lymphocytes 5 per cent., large mononuclears 5 per cent.; sputum negative for tubercle bacilli on fourteen different occasions. The temperature varied between 100 and 101 and at one time rose to 102° F.; pulse 78 to 104; respiration 20 to 32. The patient lost nine pounds during his stay in the hospital (150 to 141 pounds). The Wassermann test was negative.

Autopsy: On opening the left pleural cavity, a large amount of dark, viscid fluid escaped. The lung was soft and densely adherent to the pericardium and to the chest wall. The organ could not be separated as a whole, but had to be torn from the chest wall and mediastinum in shreds. The lung was collapsed, soft, and everywhere contained nodules which varied in size from that of a small pea to about half the size of a hen's egg. The rest of the lung tissue was soft and pulpy, and there was very little evidence of air-containing tissue. The left bronchus contained two small nodules about the size of a pea, which extended into the lung. In the apex of the upper lobe there was an encapsulated mass, about 5 cm. in diameter, from which creamy pus was expressed. The walls of this abscess were made up of white, friable tissue. There was no evidence of other abscesses. The right lung was free in the pleural cavity, without adhesions, and was readily removed. On section, the greater part of the lung was air-containing, but throughout there were small, hard nodules which varied in size from that of a pea to about half the size of a hen's egg. The intervening lung tissue was dark red in color but crepitant. The right bronchus showed no evidence of infiltration. The pleural cavity contained no fluid and no adhesions.

Anatomical Diagnosis. Lungs—carcinoma; chronic fibrinous pleuritis; atelectasis; abscess; acute bronchitis; carcinoma of bronchus (left).

Microscopic Examination: Microscopically the lungs showed large, pale staining cells, with prominent nuclei, appearing in cords or strands, and occupying the lung alveoli. There was but little of a connective tissue framework present. The nodules in the right lung were similar to those in the left. Microscopic diagnosis: Carcinoma arising from mucous glands of left bronchus.

Case 4. Adult male, fifty-one years of age, married, American, admitted to Bellevue Hospital September 9, 1920, died September 14, 1920. The patient stated that he had been engaged in newspaper work since he was twenty-one years of age; he smoked a moderate amount of cigarettes and took alcohol occasionally; he had measles and diphtheria during childhood; wife and one child alive and well.

The onset of the patient's illness occurred in February with grippe, at which time he was confined to his bed for one week. Since then, he suffered from cough, dyspnea, pain in chest, chills, fever, and night sweats; lost weight and strength; moderate expectoration, anorexia, no hemoptysis.

Physical Examination: The patient appeared to be well developed and well nourished, but chronically ill. The lungs showed very little expansion on the right side; posteriorly vocal fremitus was absent from the midscapular region to the base; there was flatness over the same area and no breath sounds; above this area there was harsh breathing with few râles. Respirations were impaired at the apex on the left side and there were compensatory breath sounds throughout the left lung. The liver was palpable and there was a mass in the lower hypochondriac region, firm and slightly nodular, moving on respiration. Twelve hundred c.c. of blood-tinged fluid were removed from the right side on September 10, and 300 c.c. of similar fluid were removed from the left side on September 11.

X-ray examination showed the right chest to be apparently full of fluid; the left chest showed two rounded areas of consolidation; diagnosis, metastatic lung tumor. X-ray of the kidney showed nothing abnormal. On the day before death occurred, the patient became very weak, the pulse rapid and the temperature subnormal.

The sputum was negative for tubercle bacilli on three examinations. The pulse varied between 120 and 130; temperature 97° to 98° F.; respirations 24 to 34. The urine showed a trace of albumin and granular casts; Wassermann reaction negative.

Diagnosis: Carcinoma of stomach with metastases in lungs; tuberculosis; effusion on right side.

Autopsy: On opening the chest, the pericardium was pushed over to the left of the mid-sternal line. The right pleural cavity was filled with a sero-sanguinous fluid which had pushed the right lung (atelectatic) into the cardio-hepatic angle. The excessive amount of fluid explained the descent of the diaphragm.

The left lung was removed easily, and was about normal in size. At the apex, however, there was a large, firm nodule, about the size of a plum. In the center of the upper lobe was a smaller nodule about the size of a walnut. The rest of the upper lobe was crepitant. In the lower lobe there was a hard nodule, about the size of a plum, but the rest of the lung was crepitant. On section, these nodules were composed of whitish, somewhat soft tissue, and had an irregular outline. The pleura was smooth and glistening.

The right lung was small and pushed into the cardio-hepatic angle. Only the periphery of the organ was crepitant and seemingly not involved. The inner half was made up of new growth. The mediastinal lymph nodes were involved and appeared as large, white conglomerate masses. These lymph nodes were so intimately associated with the tumor growth of the lung that lymph nodes and lung had to be removed en masse. The right pleural cavity contained about two quarts of sero-sanguinous fluid. The pleura was studded with cluster-like white growths, most marked on the lateral and diaphragmatic surfaces. The bronchus on the right side was thickened, white and of a fibro-cartilaginous consistence, and merged with the lymph nodes and extended into the lung.

The right kidney was of normal shape and size. The capsule stripped easily and exposed a smooth surface. Differentiation between cortex and medulla was well shown. The substance of the kidney was firm to the touch. The left kidney was about twice the normal size and to it was attached a large amount of fatty tissue. On section, the cut surface showed the medulla to be replaced by a mass of yellowish-white, soft material. The growth had infiltrated the upper pole, but in the lower part there was a zone of intact cortex. The capsule was so intimately attached to the growth that it was difficult to distinguish it and to peel it off.

Anatomical Diagnosis: Carcinoma of right lung with metastases in mediastinal lymph nodes, pleura, and left lung; atelectasis (right); hydrothorax (right); apical adhesions of left lung; metastatic carcinoma of left kidney.

Microscopic Examination: Microscopically, the lung tumor was similar in appearance to the one described in the last case. The kidney metastases in their morphology were similar to those of the lung. Microscopic diagnosis: Carcinoma arising from mucous glands of right bronchus.

Case 5. Adult male, thirty-eight years of age, Irish, married, electrician by occupation. Family history: father died as the result of an accident, mother of old age, one brother died of pneumonia and one sister during childbirth; one sister living. The patient stated that he drank tea and smoked tobacco excessively, but had not taken alcohol in eight years; he had gonorrhœa twenty years ago. His illness began on November 19, 1919, with cough and pain in right chest and thick yellowish expectoration. In December of the same year the sputum became streaked with blood; the expectoration was greatest in the morning. The patient lost considerable weight (dropped from 175 to 145 pounds in four and a half months) and became pale.

Physical Examination. There was marked dullness over the upper third of the right chest anteriorly and from the apex to the spine of the scapula posteriorly. The chest was asymmetrical and there was diminished expansion of the right side. The percussion note was dull over the upper part of the right chest, and extending down to the second rib and behind to the spine of the scapula. The breathing was high pitched over this area and many coarse and fine dry râles were heard. The heart was situated in the third space, extending two and three-quarter inches to the right and two and one-half inches to the left. Fluoroscopic examination showed almost complete consolidation of upper half of right upper lobe, with a cavity about the size of a small onion situated anteriorly, about opposite the third rib, this cavity being partly filled by fluid. No physical signs of a cavity could be made out. The patient expectorated about four ounces of sputum per day. These symptoms continued, the patient losing weight rapidly. He had three severe attacks of pulmonary hemorrhage, succumbing to the last attack quite suddenly on October 8, 1920.

The sputum was examined fourteen times for tubercle bacilli with negative results. The urine showed a faint trace of albumin and an occasional granular cast. Blood count showed white blood cells 19,200; polymorphonuclears 82 per cent., transitionals 1 per cent., lymphocytes 14 per cent., eosinophiles 3 per cent. The temperature was 102° F. on admission, but remained normal during his stay in the hospital. The Wassermann reaction was negative on two occasions.

The patient was first seen in December, 1919, when fluoroscopic examination showed a small dense shadow at the hilus of the right lung, about 1.5 cm. in width by 4 or 5 cm. in length. Subsequent frequent fluoroscopic examinations showed this shadow to expand and cover the upper lobe as a more or less concentric mass, the shadow becoming darker as time went on.

Autopsy: On opening the chest, the left pleural cavity was normal. The right pleural cavity was almost completely obliterated by fibrous adhesions which were markedly firm and almost stony hard in the region of the upper lobe in the posterior portion. The thymus was replaced by fat.

The left lung in the gross was normal. The right lung was removed with difficulty and its surface was covered by fibrous bands. Along the upper lobe it had become a dense, white, almost calcific blanket. On section of the lung, two abscess cavities were found, one in the upper lobe, the other in the lower lobe. Both these abscess cavities measured, roughly, 8 to 10 cm. in diameter, though the one in the upper lobe was larger than that in the lower lobe. Both cavities contained a mass of blood clot. The cavity in the upper lobe situated near the lower margin was lined with a whitish flake-like substance, friable and easily removed. There was no firm delineating membrane surrounding either cavity. The remainder of the upper lobe was hard. On section, it was of a grayish, opaque appearance, and through it radiated massive streaks of fibrous tissue arising from a dense white structure at the hilus This firm mass was found connected with the primary upper right bronchus from which it apparently took origin. The bronchus was completely surrounded by tumor tissue and finally merged with it. The abscess in the lower lobe was situated near the upper portion and, except for blood clot, it contained nothing worthy of record. There was, however, very little odor to the organ. The lower portion of the lobe was slightly congested. The middle lobe was somewhat compressed and firmly bound to the upper and lower lobes by dense adhesions. The branches of the bronchi contained blood clot and were streaked with blood. Hemorrhagic foci in the abscesses could not be determined.

Anatomical Diagnosis: Epithelioma of lung and bronchus (right); abscesses of lung (secondary); chronic interstitial pneumonia; chronic adhesive pleuritis; pulmonary osteo-arthropathy.

Microscopic Examination: Microscopic sections taken from several areas of the lung and bronchus showed a very cellular, squamous cell tumor in which there were typical pearl formations. Microscopic diagnosis: Epithelioma of right lung arising from the right bronchus.

W. G. MacCallum (*Text-Book of Pathology*, p. 961) refers to a series of primary lung tumors, among which were several instances of a large cavity in the lung, lined by opaque, yellowish-white, friable, crumbling tissue, in some of which the bronchus could be traced directly into the cavity, its wall becoming thickened by a new growth of the mucosa, which became continuous with the margins of the lining of the cavity. Microscopically, the tumor was made up of strands of atypical stratified epithelium, showing all the characteristics of cutaneous cancers. MacCallum believes it may be an example of metaplasia, but also suggests that it may be dependent upon an embryonic displacement of cells destined to become squamous epithelium. These tumors seem to be in accordance with the one which we encountered.

Case 6. Adult male, forty-one years of age, married, a packer by occupation, admitted to Bellevue Hospital April 3, 1920, died June 18, 1920. The patient's father died at the age of sixty, cause unknown; mother died at fifty-five of stomach trouble; two sisters died at the ages of twenty-seven and twenty-nine, respectively, cause unknown. Previous history—the patient had had measles, pertussus, bronchitis, scarlatina; in adult life, recurrent bronchitis; operative—circumcision and varicocele; had gonorrhœa at the age of twenty, no lues. Habits: drank coffee, tea, whiskey and beer; bowels regular; nocturia for past three or four years.

The onset of his illness occurred in December, 1919, with pain in the right chest posteriorly, in the scapular region; was strapped by a doctor and told to go back to work. Two weeks later, he stopped work again and rested for three weeks on account of pain in chest, fever, and cough with expectoration. His sputum was examined on three occasions and found negative for tubercle bacilli. At the end of three weeks, he felt better and returned to work for two days, when symptoms recurred, and then he noticed swelling of the veins of the neck. He went to a hospital, remained there forty-seven days, and was then referred to Memorial Hospital for treatment of tumor of chest. X-ray at the first hospital was negative for new growth. Dyspnœa became gradually marked, also headaches, vertigo with coughing and numbness and tingling in left arm after violent coughing. He lost about twenty pounds in weight in four months.

Physical Examination: There was no cyanosis or dyspnœa in the recumbent position. The veins of the neck, back and arm were dilated and prominent. There was no limitation of expansion of the lungs and tactile fremitus was diminished at the right base posteriorly and laterally. There was flatness over the same area, and harsh vesicular breathing at the right apex posteriorly, just above the area of flatness. The breath sounds were broncho-vesicular, almost bronchial, and were absent at the base. Normal vesicular sounds were heard over the left chest. Heart—apex beat not visible; faintly palpable with point of maximum intensity in the fifth space, three and three-quarter inches from mid-sternal line; no thrills; no enlargement by percussion; no murmurs; pulses regular. The abdomen was negative on external examination. The axillary and right cervical lymph nodes were palpable. On May 20, 100 c.c. of clear straw-colored fluid were removed from the right chest; on June 6, 125 c.c. were aspirated and on June 17, 625 c.c. of reddish clear fluid were removed (sp. gr. 1.018, much fibrin). On May 27, right hemiparesis was noted, also slight motor aphasia. On June 15, the patient became drowsy, but was still rational, with frequent hiccough.

Three X-rays were taken: the first showed pleural effusion (4/9/20); the second, interlobar abscess between right upper and middle lobes, effusion in right costo-phrenic space (5/17/20); the third, new growth of lung with pleural effusion, no metastasis in bony skull.

The urine was negative; Wassermann reaction on blood and spinal fluid negative; colloidal gold reaction on spinal fluid negative. The temperature varied between 99.8° and 102° F., averaging about 101°; respirations 18 to 32; pulse 88 to 120.

On June 18, the patient died.

Autopsy: The right pleural cavity was distended by pale brownish-colored fluid in the form of pockets. The right lung was everywhere firm to the touch and it was chiefly adherent over the sides. The costal pleura was thickened and on the pleura near the sixth and seventh ribs there was a firm tumor mass, whitish in color, measuring about one inch in diameter. The right bronchus was everywhere infiltrated with firm, white tumor growth. The upper lobe was bluish red in color and presented a number of what appeared to be abscesses of smaller size. The lower lobe contained in its center a considerable amount of softened, whitish material, resembling the appearances of a lung undergoing resolution. The left lung showed compensatory emphysema and the upper lobe was large and extended somewhat over the middle line. Section presented no other appearances than that of congestion; the bronchi were normal in appearance except for congestion of the mucous membrane.

Anatomical Diagnosis: Primary tumor of right bronchus with metastases in right cerebellar lobe and right kidney.

Microscopic Examination: Microscopically, the tumor, as well as its metastases, presented large, clear, pale staining cells, similar to those found in the above described bronchial growths. Microscopic diagnosis: Carcinoma of right bronchus.

Case 7. The patient was a woman sixty-six years of age, who was admitted to Bellevue Hospital February 9, 1921, and died February 27, 1921. She stated that she had lost considerable weight during the past year (exact amount not known); appetite was poor, and bowels constipated. She also stated that she had been operated on for cystocele (date not given). The onset of her illness occurred four weeks previous to admission to the hospital, characterized by pain in the left side of the chest, with coughing and gradual loss of strength and weight. Associated with this condition she developed edema of the lower extremities with some arthritis of the left hip; she expectorated small amounts of dark rusty sputum.

Physical Examination: Revealed an elderly female, weighing about 110 pounds, poorly developed and nourished. The skin was dry and scaly; no palpable adenopathies; marked anæmia. The pupils reacted to light and accommodation. The patient held her head forward as though too weak to support it and there seemed to be some separation between the seventh cervical and first dorsal vertebræ. The thorax was poorly developed and no apex beat was visible. There was some dullness with increased breath sounds over the left upper lobe and crepitant râles over the right middle lobe anteriorly and in the left axilla in the fifth and sixth interspaces. The heart was not enlarged; there were no murmurs; the sounds were distant and of poor quality and the vessels sclerosed. The liver was felt two fingers' breadths below the costal margin; the spleen and kidneys were not palpable. There were no varicosities or ulcers of the lower extremities; the knee jerks were normal; no Babinski or Oppenheim. On February 10, many crepitant and subcrepitant râles were noted, with dullness and distant bronchial breathing over the left infraclavicular region, and on February 26, there was consolidation of the left lobe.

The urine was amber-colored, sp. gr. 1.010, reaction acid, albumin faint trace, glucose negative, granular casts, few red blood cells. Blood count: Leucocytes 6,800, number of cells counted 50, polymorphonuclears 70 per cent., transitionals 3 per cent., lymphocytes 27 per cent. The Wassermann reaction was negative; the sputum was negative for tuberculosis. The temperature was 101.6° F. on admission and varied between 98.4° and 103.4°. The pulse varied between 110 and 140.

Clinical Diagnosis: Chronic interstitial pneumonia

Autopsy: On opening the chest, the precordial area appeared normal in size, the right border being overlapped by the edge of the right lung. The right pleural cavity had scattered strands of loose fibrous adhesions over it. The left pleural cavity had many easily broken down adhesions extending over the upper lobe. Both cavities were dry.

The lungs did not collapse completely when removed. The surface of both lungs presented a lobulated appearance. Smoothly rounded lobules, 1 to 3 cm. in diameter, were marked off by deep fissures so that the appearance was similar to that of a hobnailed liver with very large knobs. This lobulation extended throughout practically the whole of both lungs, but was less marked at the extreme base. The lungs were heavy and felt moderately firm, except for the extreme right base and the lower third of the left lobe. Each individual lobule had superficially the light cottony feeling of the emphysematous lung, but on deeper pressure, firmer tissue was felt. The surface was light gray and mottled with anthracotic pigment. The pleura, except in the fissures described, had a smooth glistening appearance but not on the right diaphragmatic surface, and between the right middle and lower lobes. Here it had lost its luster and there was an adherent exudate of greenish fibrin. On section, the lung presented a dirty gray appearance, imperfectly aerated, and a number of dilated spaces containing greenish-yellow pus. These were lined by a definite membrane, and one or two admitted a probe for some distance, suggesting that they were bronchiectatic. The smaller bronchi exuded pus on pressure.

The liver was normal in size. The capsule was thin and tense and somewhat adherent to the diaphragm and transverse colon. One fibrous nodule, about 0.5 cm. in diameter, was visible beneath the capsule on the anterior surface. On section, it cut with resistance and extended into the liver tissue.

Anatomical Diagnosis: Right lung: organizing pneumonia; adenocarcinoma; acute fibrinous pleuritis; bronchiectasis; emphysema; purulent bronchitis. Left lung: fibrinous pleuritis; interlobar empyema; purulent bronchitis; bronchiectasis; emphysema; organizing pneumonia; adenocarcinoma. Liver: corset liver; metastatic nodule (adenocarcinoma); perihepatitis.

Microscopic Examination: Sections from the lung showed a fibrous tissue hyperplasia in places, together with many areas of prominently defined epithelial growths scattered throughout both lungs. Microscopic diagnosis: Carcinoma arising from the finer bronchioles in the lung.

The diagnosis of primary lung tumors presents one of the most interesting as well as one of the most difficult problems in clinical medicine. The possibility of metastases from a symptomless growth in an esophageal diverticulum or a small growth in the gall-bladder, thyroid, etc., is always well worth considering.

No positive diagnostic criteria are known. Frequent examinations with the fluoroscope are most apt to reveal a progressive growth.

Discussion:

Dr. Larkin: It is difficult to discuss primary tumors of the lung. One of the present specimens is a large tumor centrally located which has all of the characteristics of tumors which are primary in the bronchi. The other specimen seems not to be connected with the lung, but is a tumor which is invading the lung secondarily and is primarily a pleural neoplasm. It has that very peculiar character of incrusting the pleura, sending ramifications into the lung and along the bronchi. These tumors are interesting, not only because of their pathological rarity, but also because of the clinical phenomena during the life of the patient. I have in my collection six or eight tumors like the specimens shown here, and the more I have studied the histology of the type of tissue in order to arrive at a conclusion as to where the tumor originated, the more I am bewildered. The tumor, with the incrustation, seems to me to be a tumor primary in the pleura, for it has the physical characters of ramifications and the incrustation of the pleura and the involvement of the bronchi. These tumors may be diagnosticated from physical evidence during the life of the patient, for they are usually accompanied by large amounts of pleural exudate, generally hemorrhagic in type. A number of years ago Dr. Ewing made a diagnosis of primary endothelioma of the pleura from a centrifugalized exudate. Only recently I have seen a case in which a large amount of hemorrhagic fluid was withdrawn from the pleura and on examination of the centrifuged sediment there was no question of the diagnosis of endothelioma. At autopsy a tumor of the right lung was found, which is exactly similar to the specimen shown here to-night.

Dr. Moschcowitz: I do not think the diagnosis of primary tumors of the lung is quite as difficult as Dr. St. George makes it out. The majority of tumors of the lung seem to be of three types: first, those that resemble mediastinal tumors, and I think these are mostly primary tumors at the hilus of the lung arising from the bronchus. I should like to call attention to an early and characteristic sign, and that is the fixation of the trachea. It has very little lateral and vertical mobility. The second form in which tumors of the lung may present themselves clinically is that where you find a solid mass situated in one or the other lung. The third type simulates pleurisy with effusion and this is the one which I think offers the most difficult problem in diagnosis. I find that you can often make a diagnosis much better by taking the centrifugalized fluid, fixing it in formalin so that it comes out a gelatinous mass from the bottom of the test tube, and running it through paraffine. The chances of finding tumor cells are far better than by simply making a smear.

Dr. Ewing: This winter I have seen at autopsy two cases of epithelioma of the lung arising on tuberculous bronchitis—highly malignant squamous carcinomas. The proportion of cases Dr. St. George found free from tuberculous lesions is unusual. I wonder whether he has thoroughly searched the tissues for tuberculous lesions.

Dr. Larkin: Do I understand Dr. Ewing to say that there is a connection between tuberculosis of the peribronchial tissues and the malignant growths?

Dr. Ewing: In these cases there were active tuberculous lesions in the lungs from which the epithelioma developed.

Dr. Larkin: Were the tumors of any great size?

Dr. Ewing: No.

Dr. Larkin: Was the diagnosis macroscopical or microscopical?

Dr. Ewing: Both.

Dr. St. George: In answer to Dr. Ewing's question as to whether we searched the tissues for tuberculosis, we did. The only one that showed any evidence of tuberculosis was the sarcoma case and that had some nodules at the apex.

As regards the diagnosis of these tumors, I do not want to convey the impression that it is so exceedingly difficult, although to differentiate a primary lung tumor from a metastasis is difficult to some extent. Recently at a meeting here in New York a clinician said he had diagnosed thirty lung tumor cases, but all without an autopsy; hence whether they were correct diagnoses is a debatable question. We have presented only those cases of primary lung tumor which can be proved beyond doubt to be so. Dr. Norrie has seen a number of these cases at the hospital and even in the patient where the shadow was observed growing from the lung he was not willing to make a diagnosis of tumor, but held to his diagnosis of abscess. He would not say whether they were primary lung tumors, or were metastatic. In the autopsy service at Bellevue the percentage of tumors metastasizing into the lung is rather large, and we hesitate to make a diagnosis of primary lung tumor.

I do not know which specimen Dr. Larkin referred to as being an endothelioma, but I believe it is the one which I had seen six weeks after onset of symptoms and which showed the shadow at the hilus. I knew the man very well and followed him up. In another hospital they had made a diagnosis of tuberculosis in his case, largely I believe because they obtained a + + + + tuberculous complement fixation. I had him fluoroscoped repeatedly during the following months, and we found the shadow to grow out and into the lung. I think it is fair to assume that it is a bronchial growth. Some of the sections are suggestive of the tumor starting from the glands of the bronchus.

THREE BRAIN TUMORS

NATHANIEL B. STANTON, M.D.

(From the Laboratory of the Lenox Hill Hospital, New York City)

In his text-book on Neoplastic Diseases, Ewing states that probably one per cent. of all deaths are due to brain tumor, while Tooth in an analysis of 632 cases gives as the relative frequency in location: tumors of the brain proper 94 per cent., of the pituitary 2 per cent., and of the pineal gland less than one half of one per cent. Based on an analysis of 434 cases, the frequency of various histological types is tubercle 183, gumma 45, sarcoma 113, glioma 127, osteoma 4, and cholesteoma 2.

The cases recorded in the present report are of the pituitary and pineal glands. Of the various histological types encountered in the pituitary gland the order of frequency is diffuse hyperplasia with focal adenoma, adenocarcinoma, and last sarcoma. An analysis of sixty-eight cases of pineal tumor gives as the most common types in the order of frequency: cysts either with or without tumor growth, teratomata, and finally ependymal glioma.

The general symptomatology of cerebral neoplasms may be considered under three headings: (*a*) symptoms common to all tumors, such as headache and evidence of increased intracranial pressure; (*b*) localizing symptoms, such as paralysis; (*c*) symptoms due to disturbance of special function associated with neoplasms of the pituitary and pineal glands.

The special symptoms arising from neoplasms in the pituitary may be divided into two groups: (1) the cephalic type, in which pressure symptoms are predominant; (2) the dystrophic type, in which disturbances of growth are prominent symptoms. In the cephalic type the chief complaints are headaches, dizziness and paralyses, or interference with other portions of the visual apparatus. The dystrophic type may again be divided into four groups: giantism with or without acromegaly, infantilism, acromegaly, and that condition spoken of as adiposis genitalis.

The tumors of the pineal gland show as endocrine disturbances: hypertrophy of the sexual organs, overgrowth of the pubic hair, and precocious sexual instinct.

The first case, that of a pituitary carcinoma, has the following history. A male, age sixty-two years, complained of severe pains in the abdomen lasting for the past six weeks. This pain was continuous, burning in nature and did not radiate; it was made worse by eating and was not relieved by vomiting. There was no hematemesis. There were also present a slight cough and considerable loss of weight. He had had severe headaches and a ptosis of the right eye for three weeks, and a ptosis of the left eye for a short time about five weeks previous to admission.

Physical examination showed the following pathological conditions: emaciation; the right pupil dilated, irregular and sluggish in reaction; a divergent squint; diplopia; and atrophy of the optic nerves. During his illness all ocular nerves except the external rectus of the left eye became paralyzed. There was a palpable tumor mass in the left upper quadrant of the abdomen. The abdominal and cremasteric reflexes were absent and there were shooting pains in both legs.

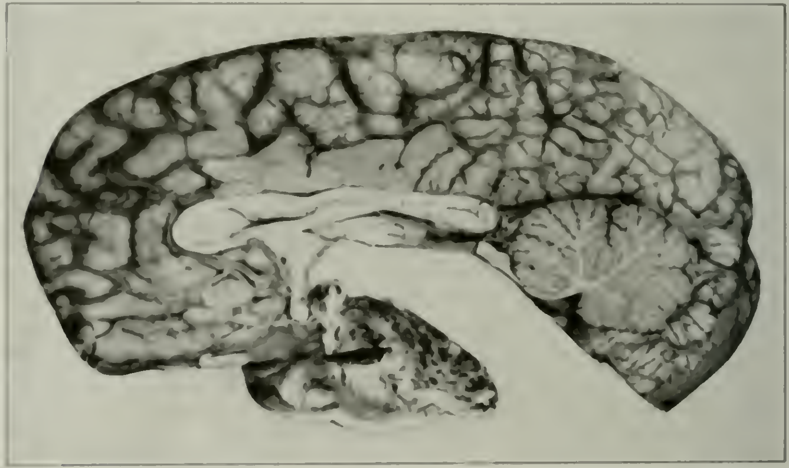


FIG. 1.

X ray examination showed erosion of the sella turcica and destruction of the clinoid processes, and in addition a large, dense, irregular consolidation at the root of the right lung which increased in size very rapidly as shown by later pictures. Further radiographic examination showed a constant deformity in the prepyloric region of the greater curvature of the stomach. Gastric analysis showed an absence of free hydrochloric acid and a total acidity of nine. The blood sugar was 81 milligrams per 100 c.c.

The unusual features found at autopsy were several. At the hilus of the right lung there was an irregular neoplasm which involved the large vessels and the main bronchi and which measured 13 cm. in the greatest diameter. The central portions of the growth were necrotic. All of the mediastinal nodes were involved in a neoplastic process and matted together the lungs and heart. The head and the larger portion of the body of the pancreas were replaced by neoplastic tissue. There were several metastases in the mesentery and omentum, the largest measuring 8 cm. in diameter. In the mucosa of the stomach at the greater curvature near the pylorus, there were three metastases, the largest of which was a sessile mass 3 cm. in diameter. Both adrenals showed metastatic deposits and there were growths in the spleen and in one kidney, as well as several neoplastic deposits in the skin and subcutaneous tissue.

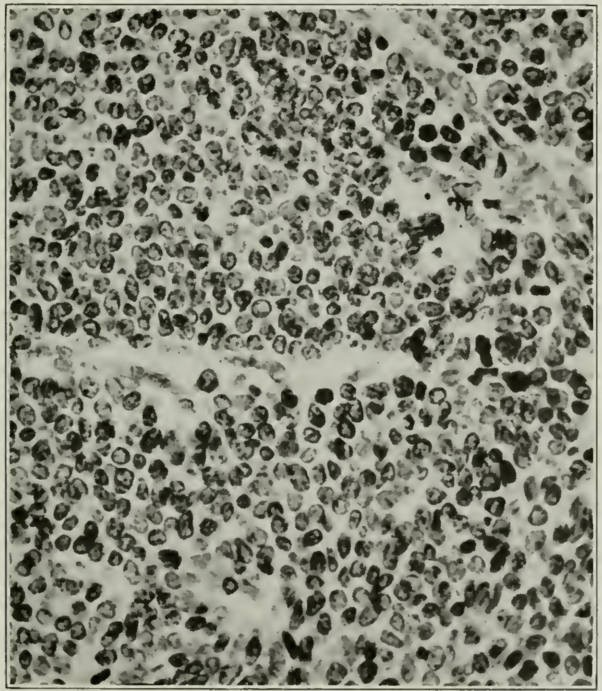


FIG. 2.

The convolutions of both hemispheres of the brain were markedly flattened and the pia arachnoid showed a marked edema. In the region of the pituitary gland there was a soft mushy neoplasm which had very extensively eroded the sella turcica, and which was tightly adherent to the bone and meninges and which by direct extension had invaded the optic commissure. Both lateral ventricles were much distended and contained excessive amounts of fluid. In the position of the third ventricle (Fig. 1) there was a dark, red, smooth, globular mass, 4 cm. in its greatest diameter and which had a sessile base. Section through the mass showed that the base extended through the brain and was continuous with the neoplasm involving the pituitary gland.

Microscopic examination showed the tumor to be a small cell epithelial neoplasm (Fig. 2) whose architecture, particularly in the primary growth in the pituitary, was that of a papillary form, the cells being about a center core consisting of a thin walled blood vessel supported by a loose connective tissue. Areas of necrosis were relatively common. In sections through the pituitary the gradual transformation from the normal cells of the pars anterior to frankly malignant cells was demonstrable.

The interesting phases of the case were the absence of evidence of disturbed endocrine function, the widespread metastasis, and the absence of disturbances in sugar metabolism as evidenced by a normal blood sugar and absence of sugar in the urine, this in spite of widespread lesions, which involved pancreas, adrenals and pituitary.

The second case of pituitary tumor, also a carcinoma, occurred in a male aged eighteen years. He was admitted to the hospital because of persistent headaches, gradually developing blindness and paralysis of the third and ocular branch of the fifth nerves on the right side. There was somnolence and loss of weight. The X-ray examination showed no erosion of the sella turcica. The evidences of disturbed endocrine function were emaciation, absence of axillary hair, poorly developed genitalia, a fine smooth skin and the general appearance of a youth about five years younger than his given age.

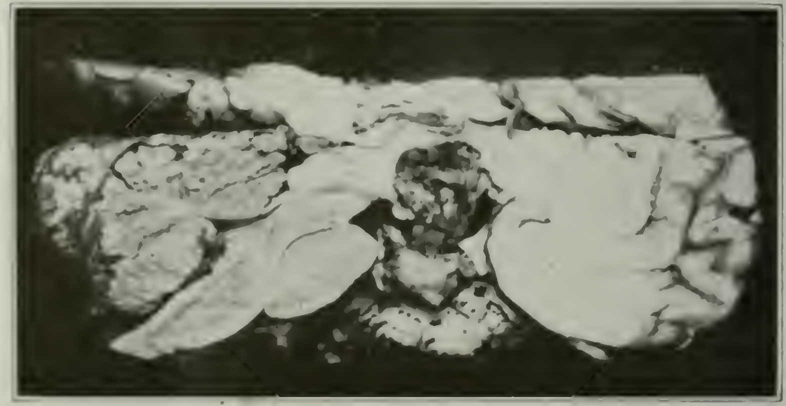


FIG. 3

Upon opening the skull a large amount of clear cerebro-spinal fluid escaped. The convolutions of the right forebrain were found to be markedly flattened. The pituitary was replaced by a soft hemorrhagic mass which had almost completely destroyed the clinoid process of the right side and had eroded the saddle of the sella turcica so that there was an opening into the sphenoidal cells (Fig. 3). The mass was tightly adherent to the meninges and measured 2.5 x 1.75 cm. Both lungs showed small hemorrhagic infarcts. The testes were atrophic. The other organs were of no particular interest.

The microscopic examination of the second tumor showed a carcinoma of the alveolar type (Fig. 4) though the individual cells were of the same general character as the first tumor described. The alveoli were of varying size and while in some areas definite lumina were demonstrable, in others cellular proliferation had filled the lumina. There were extensive areas of hemorrhage and smaller areas of degeneration.

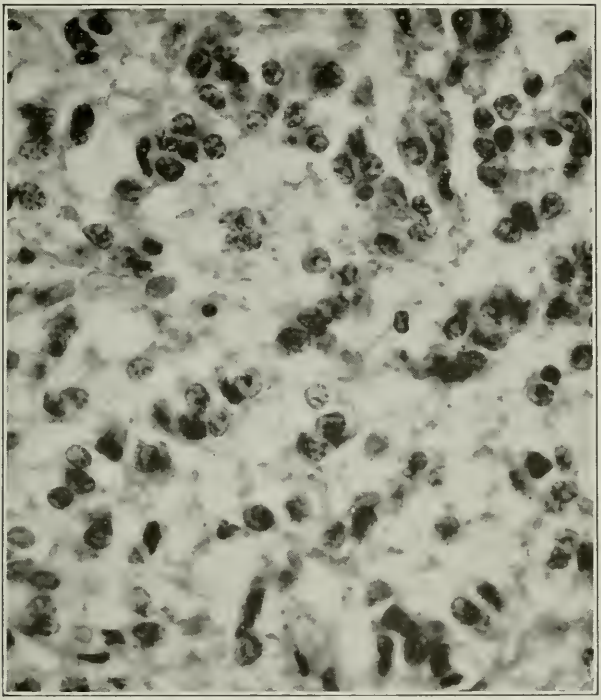


Fig. 4.

In marked contrast to the first case, the second instance showed no metastasis and gave evidence of endocrine disturbance.

The third case of this series was a multiple cyst of the pineal gland discovered accidentally at autopsy and giving rise to no symptoms during life. A male, twenty-six years of age, complained of pain in the back of the neck and shortness of breath for five weeks. The pains were throbbing, radiated to the occipital region and kept him awake at night. At the same time there were stinging pains in the fingers and toes which lasted from a few hours to a few days. There was no evidence of endocrine disturbance in either history or physical examination.

Physical examination showed a heart enlarged downward and to the left; a double mitral murmur at the apex and a diastolic murmur at the aortic area transmitted to the vessels of the neck. There were petechiæ in the conjunctivæ and skin and a blood culture showed *streptococcus viridans*. During his stay in the hospital he ran a septic temperature.

At autopsy the clinical diagnosis of malignant endocarditis was confirmed. The present interest is in the brain which was normal except for a small tumor of the pineal gland, 1.5 cm. in diameter (Fig. 5).

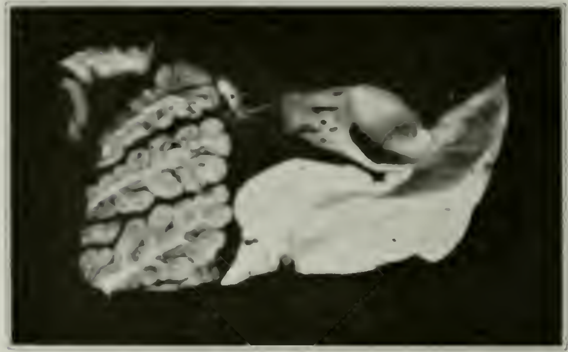


Fig. 5.

Microscopical examination of the pineal growth showed a somewhat distorted and persistent pineal gland with foci of calcification and larger and smaller cyst cavities either lined directly by the normal pineal cells, or lined by a moderately thick layer of glia tissue.

The three cases have been presented not so much for their relative rarity, but as illustrations of the extensive neoplastic destruction which on occasion may occur in one of the endocrines without giving rise to the conditions usually associated with endocrine dysfunction.

Discussion.

Dr. Ewing. I would like to ask what was the structure of the abdominal and other metastases in the second case. It is very rare to have so many metastases from pituitary tumors.

Dr. Rothenberg. The morphology of the metastases was the same as that of the original tumor. Metastases were present in practically every organ of the body.

Dr. Ewing: Was the structure of the pituitary tumor characteristic of any you have seen before in the pituitary?

Dr. Rothenberg: The morphology of the primary tumor was typical of other pituitary tumors which I have seen.

FIBRO–SARCOMA OF THE APPENDIX

G. L. ROHDENBURG, M.D.

(*From the Pathological Laboratory, Lenox Hill Hospital, New York City*)

While epithelial neoplasms of the appendix, even though they are seldom clinically malignant, are not infrequent, neoplasms arising in the other types of tissue present in the organ are relatively rare. If chronic irritation is the important factor in tumor genesis, as is currently supposed, it would not be at all strange to see malignant change in the organ, for in relatively few individuals is there absence of evidence of chronic inflammation. Possibly the apparent rarity of clinically malignant tumors in this situation may be explained by the fact that in the vast majority of cases the chronic inflammation becomes acute and the offending focus is removed, either before the cancer age or before the irritation has persisted for a sufficiently long period.

The present case is that of a male, aged seventeen years, admitted to the hospital on the service of Dr. George Semken. His family history was strongly tubercular, and the patient himself stated that three months before admission he suffered from a cough, was feverish, and had profuse night sweats. With the exception of his cough the symptoms remained and two weeks before admission he noticed a mass in the region of the appendix. The only clinical and laboratory data of positive nature were the presence of a rounded mass, freely movable, in the region of the appendix, a septic type of temperature, and a radiographic finding that the tumor was attached to the cæcum. Tuberculosis could not be demonstrated either radiographically in the lungs or by various laboratory examinations. At a laparotomy a rounded, reddish tumor was found attached to the cæcum where the base of the appendix should have been, the omentum being attached to the edge of the tumor. The growth was extremely vascular, receiving its chief nutrition from the omental attachment.

The tumor measured 13 x 10 x 12 cm. and, as previously stated, attached to one surface was a broad band of omentum containing many large-sized blood vessels. At the other pole projected the lumen of the appendix which was patent throughout.

Microscopically the tumor was found to be composed largely of small spindle-shaped cells embedded in a fibrillar matrix (Fig. 1), which was scanty or fairly abundant and richly infiltrated with small round cells.

Spindle cells were fairly numerous and were spread diffusely throughout the tumor or arranged in parallel or interlacing bundles. Among these cells were a few larger cells of round or spindle shape with hyperchromatic nuclei and acidophile protoplasm. The tumor contained many small blood vessels and capillaries.

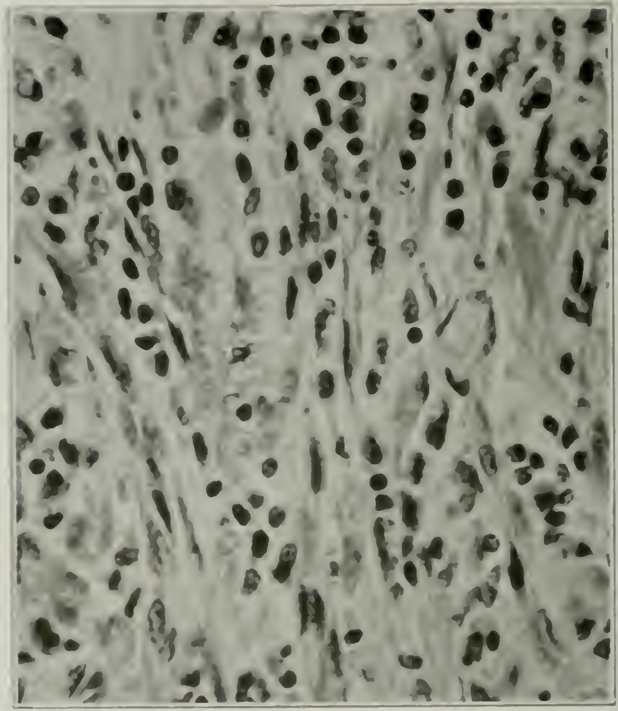


FIG. 1.

The case is interesting from the standpoint of diagnosis, for with a familial history of tuberculosis, an onset of distinctly tubercular type and a mass in the ilioc&aelig;cal region, the differential diagnosis between ilioc&aelig;cal tuberculosis and neoplasm was not easy.

A TUMOR OF THE LEFT AURICLE

P. D. HOFFMAN, M.D.

(From the Pathological Laboratories, Bellevue and Allied Hospitals, Dr. Douglas Symmers, Director, New York)

The rare incidence of primary tumors of the heart is illustrated by the fact that in 3,000 autopsies at Nüremberg, Thorel did not encounter a single one; the Bellevue Hospital records of over 7,000 autopsies include no cases.

One of the first collections of primary tumors of the heart was made by Berthenson, who, in 1893, reported 28 cases of the following varieties: sarcoma 9, myxoma 7, fibroma 6, carcinoma 3, lipoma 2, cyst 1. As to location, 7 were in the right auricle, 3 in the right ventricle, 7 in the left auricle, 5 in the left ventricle, and 4 in the septum.

Link, in 1909, collected 91 cases; on some of them, however, the data were scanty, so that all may not be authentic. Myxomata and sarcomata are the most frequent cases in his series. In addition to this series, 11 cases of rhabdomyoma were collected by Wolbach in 1907.

Karrenstein's collection, in 1908, included 39 cases, excluding myxoma, and 38 cases of myxoma. This collection is of interest in regard to the location of the tumors. He finds that in the case of myxomata the left auricle is the most frequent site, while out of 6 cases of sarcoma 5 were located in the right side of the heart.

According to recent literature, the myxoma is the tumor of far the most frequent occurrence. A case of this tumor was reported before this Society by Louria in 1917. Thorel believes many of these reported as myxomata are in reality thrombi that have undergone myxomatous degeneration. He likewise rejects many reports of fibroma as being organized thrombi.

The first case of primary sarcoma was reported in 1865 by Bodenheimer. This case had been observed clinically and brings up the interesting question of the diagnosis of cardiac tumors.

No cardiac neoplasm has thus far been diagnosed during life. The diagnosis in this case most nearly approached a correct one. It was: "Cardiac disease of unknown origin."

The reason for the difficulty in diagnosis lies in the fact that there are no symptoms characteristic of cardiac tumors, but these resemble the symptoms of any form of cardiac disease and their character depends upon the size and location of the tumor. It has frequently been observed that there may be no symptoms referable to the heart, and the condition is discovered unexpectedly at autopsy. A number of writers have cited symptoms which they believe should be suggestive of a tumor of the heart. Thus Fraenkel considered bloody pericardial effusion, in the absence of tuberculous or scorbutic disease, a certain sign of cardiac neoplasm. This has, however, not been observed in any cases other than his own. Berthenson (1893) lays emphasis on embolic manifestations, but others consider these unusual in cardiac neoplasms. He also discusses murmurs, which may or may not be heard, and which, if present, may not be so clear as in endocarditis and may vary in intensity. Others mention exclusive involvement of one side of the heart.

The case to be presented tonight is as follows:

H. F., a male, thirty-seven years old, was operated on at Bellevue Hospital for inguinal hernia on January 18, 1921. He had never had symptoms referable to the heart and had an entirely negative medical history. On questioning, after cardiac signs were discovered, he said he had had rheumatism in the wrists several years ago. Examination of the heart showed enlargement to the left and rough apical presystolic and diastolic murmurs were heard. Compensation was so good that general anæsthesia was not contraindicated. The patient was discharged February 12, cured of the hernia, and was referred to the cardiac clinic. After he left the hospital, his feet became swollen and he was somewhat dyspnœic. He came to the cardiac clinic and was referred to the ward on March 15. The patient became rapidly more dyspnœic and cyanosis appeared. The respirations were 40. There was ascites, tympanites and edema of the feet and legs. Leucocytosis and fever were present.

Physical examination showed a well-developed man, dyspnœic but lying flat in bed. Examination of the heart showed moderate enlargement to the right and left, with the apex beat in the fifth interspace outside the midclavicular line. The heart sounds were of fair muscular quality, irregularly irregular, rate 140. A systolic murmur was heard at the apex and a diastolic murmur at the base and in the aortic area. The diagnosis was (1) chronic cardio-valvular disease with mitral stenosis and insufficiency and relative aortic insufficiency, (2) cardiac hypertrophy and dilatation, (3) auricular fibrillation, (4) congestion, bases of both lungs, (5) chronic passive congestion of the liver, (6) coronary sclerosis and thrombosis with myocarditis, (7) ascites.

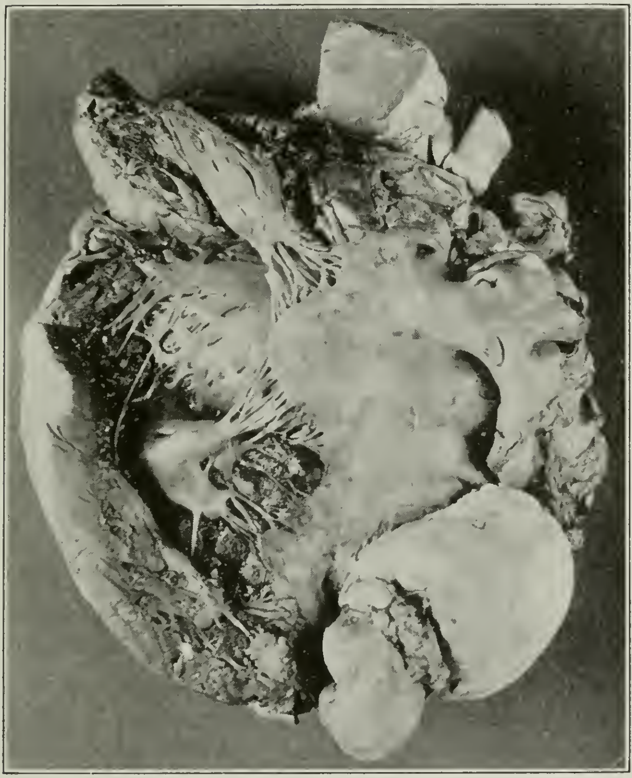


Fig. 1.

The morning after admission, at about eleven o'clock, the patient went into shock. The extremities were cold and blue, with drenching perspiration. The temperature was elevated; the pulse was not palpable at the wrist, and respirations were rapid and labored. The patient died suddenly, growing very blue just before death. The first heart sound was of good force and muscular quality within ten minutes before his sudden death.

The autopsy was performed a few hours after death. The main anatomical diagnoses were as follows: Tumor of left auricle, verrucous endocarditis of mitral valve, cardiac hypertrophy and dilatation, chronic fibrinous adhesive pleuritis, chronic passive congestion of the liver, fibroma of the left suprarenal gland, ascites, edema of lower extremities.

The pericardium was normal and contained no excess of fluid. The heart was moderately enlarged, especially the right ventricle. The right auriculo-ventricular orifice admitted three fingers easily. On exploring the left auriculo-ventricular orifice, it was found to admit only one finger, and a smooth, rounded body, slightly movable, was felt at the side of the orifice. On opening the heart, the valves of the right side and the aortic valves were found to be normal and there was no change in the endocardium. There was slight thickening of the walls of the right ventricle and dilatation of both ventricles. There were no changes in the coronary arteries. The mitral valve showed some thickening of the posterior cusp and of the attached chordæ tendineæ. The anterior cusp showed numerous small, somewhat flat, reddish, verrucous growths.

Attached to the antero-lateral wall of the left auricle was a firm, whitish mass, the size of a hen's egg. This was attached to the auricular wall for all except the lower 2 cm. of its length. The whole mass was 7.5 cm. long and 5 cm. wide at its widest part, which was about the middle. It was irregular in contour, smooth, but not glistening. The endocardium appeared to extend for about 4 mm. up the side of the mass. The lowest portion, which had no direct attachment to the auricular wall, projected into the auriculo-ventricular opening and was the rounded body felt on exploring the orifice before the heart was opened. It could be rotated slightly and in the formalin-hardened specimen is to be seen displaced upward and laterally. There was a band of rough reddish material, apparently fresh thrombotic deposit, separating the lower portion from the main body of the growth.

The mass was considered as probably a thrombus, with the possibility of its being a tumor.

Microscopic examination of sections removed from the mass in the left auricle revealed the fact that it was divisible into three zones. The lowermost zone was composed of apparently well-preserved heart muscle, superimposed upon which and constituting a second zone was a layer of fibrous tissue. The third zone presented a rather complex histology. Just above the connective tissue septum were masses of spindle-shaped cells which were arranged in whorls or bundles and which were indistinguishable from smooth muscle cells. These gradually faded into areas where all normal cell relationships were lost, the cells being irregular in arrangement and variable in size, provided with very little intercellular substance, the nuclei more or less richly chromatic, in places hyperchromatic, the whole representing, apparently, sarcomatous transformation of the supporting connective tissue. In some of the sections cells of this general type were found scattered around slit-like formations representing, possibly, dilated capillary vessels. In one of the sections, also, was a small collection of cartilage cells, some of which were evidently undergoing calcification. The presence of cartilage cells suggests the possibility that the tumor is teratomatous in nature.

Moreover, it is difficult to account for the presence in the growth of smooth muscle cells except on a developmental basis, unless one assumes, of course, that they are derived from the muscular layer of the nutrient arteries of the heart.

As stated above, the first case of primary sarcoma of the heart was reported in 1865. In 1910 Baldwin collected seventeen cases which he considered authentic, including one of his own. In 1918 Perlstein reported a case of sarcoma apparently originating from the epicardial areolar tissue. He had made a careful search of the literature, and enumerated thirty cases beside his own, omitting all those whose true sarcomatous nature appeared to him to be doubtful.

There are three interesting points in connection with the present case:

1. It illustrates the difficulty in distinguishing between a thrombus and a cardiac tumor without careful microscopic examination. The appearance of the tumor is that of a thrombus and, indeed, it consists in large part of thrombus which has been deposited on the tumor.

2. The location in the left atrium is unusual in this type of tumor. In Perlstein's thirty cases eleven were situated in the right atrium. The septal wall of the atrium is also a much more frequent site of attachment than the antero-lateral wall, which was the attachment in the present case. The septal wall is considered as having a disposition to tumor formation, perhaps from the complicated foldings and displacements which take place in development at this place (Marchand and Fuhrman).

3. The fact that the tumor projected through the mitral orifice, partially occluding it and giving rise to symptoms of mitral stenosis, is of great clinical interest. Link gives fourteen cases of cardiac tumor in which the mitral orifice was thus obstructed. In one case death was thought to be due to incarceration of the tumor in the orifice. Considering the sudden death, with extreme cyanosis just before death, such a mechanical factor may have been responsible in the present instance. Symptoms of both mitral stenosis and insufficiency were given by most of these tumors, and these were present in this case.

A case of this sort on which there was extensive clinical observation was reported by Pavlowsky in 1893. One of the most interesting facts in connection with this case was the observation that when the patient was lying down the signs were those of mitral insufficiency, while when she was examined sitting up signs of mitral stenosis were found. The patient could hardly be persuaded to assume a sitting position and was evidently in much greater distress than when lying down. At autopsy a tumor of the left auricle was found which, in the vertical position, would occlude the mitral orifice, giving rise to serious stenosis, and in the horizontal position would recede slightly, relieving the stenosis, but interfering with closure of the mitral flaps, thus causing insufficiency.

Bibliography

1. Thorel: *Ergeb. d. allg. Pathologie u. Pathologische Anatomie*, 1903, ix, 991; 1907, xi, 443; 1915, xvii, 677.
2. Berthenson: *Virchow's Archiv*, 1893, cxxxii, 390.
3. Link: *Ztschr. f. klin. Med.*, 1909, lxvii, 272.
4. Karrenstein: *Virchow's Archiv*, 1908, cxciv, 127.
5. Louria: *Proc. N. Y. Path. Soc.*, 1917, xvii, 85.
6. Baldwin, H. A.: *Jour. Am. Med. Assn.*, 1910, lv, 646.
7. Perlstein: *Amer. Jour. Med. Sci.*, 1918, clvi, 214.
8. Pavlowsky: *Berlin. klin. Wchnschr.*, 1895, xxxii, 393.

Discussion:

Dr. Pappenheimer: I should like to ask whether the smooth muscle fibers which normally are found beneath the endocardium might not be a theoretical source of origin for the muscle fibers which enter into the composition of the tumor; also whether the auricular muscle had been invaded by the growth.

Dr. Hoffman: No; there was a band of connective tissue between the muscle wall and the tumor.

Dr. Ewing: I would like to know what the histological diagnosis in this case is.

Dr. Hoffman: It is sarcoma of the left auricle.

Dr. Symmers: In view of the fact that cartilage and smooth muscle cells are present, one must consider the possibility that the tumor is a teratoma. But, as Dr. Pappenheimer has already suggested, it is likewise possible that the smooth muscle tissue represents a normal structure. It seems to me that the more probable diagnosis is that of sarcomatous transformation of the connective tissue stroma of a fibromyoma.

Dr. Ewing: It is much more cellular than any of the tumors of this sort that I have ever seen, and I think on that account it is a very important case, because it gives a much better opportunity to determine the nature of these tumors than we ordinarily have. Most of them are very edematous so that the original structure is obscured. Here we have a well-nourished, large, solid tumor, from which I think it ought to be possible to come to some definite histogenetic diagnosis. My single glance at the specimen suggests two possibilities which I hesitate to mention after such a brief study—myosarcoma or neurogenic sarcoma. It might be worth while to try to demonstrate neuroglia fibrils by special stains.

Dr. Hoffman: I ought to mention that probably the largest bulk of the tumor is composed of thrombus, so it may really be a small tumor with large deposits of fibrin.

TWO CASES OF CONGENITAL LESIONS OF THE HEART

ALEXANDER FRASER, M.D.

These cases, though showing a number of developmental defects, are primarily and essentially extremely rare forms of stenosis of the aorta. Stenosis of the aorta, as compared with that of the pulmonary artery, is rather rare, the relation being about that of one to four, and of extreme forms like those about to be presented I have been able to find a record of only three or four in the literature. Aortic stenoses are classified by Herxheimer (Schwalbe's Handbuch) as follows: (1) Those involving the conus up to the valves; (2) those occurring in the region of the ductus arteriosus; (3) general hypoplasia of the aorta.

These two cases illustrate extreme degrees of classes one and two respectively.

Case 1. This heart was taken from a well-developed and nourished male child aged five days, born of apparently healthy parents. On the afternoon of the fifth day, he became diffusely cyanotic, developed convulsions and died suddenly. Apart from the heart, the viscera were well developed and showed no evidence of disease other than passive congestion. The heart at first sight appeared to be a three-chambered organ, consisting of two auricles and one ventricle (the right), but on further dissection I found the following: (1) a large right auricle with normal entrance of the venæ cavæ, patent coronary sinus and foramen ovale; (2) a large right ventricle with thick walls and distended chamber occupying two thirds of the interior of the organ, normal tricuspid and pulmonary valves, large conus and main artery which after giving off the right and left pulmonary branches is continued as the ductus which arches downwards to form the descending aorta; (3) from about the middle of the arch of the ductus a branch about half its size is given off to the right and this in turn gives off the left subclavian, carotid, and innominate above while it sends a small branch, 1 to 2 mm. in diameter, downwards to the right of and behind the pulmonary artery where it terminates in the right and left coronary arteries with normal branching and distribution; (4) the left auricle receives the pulmonary veins normally. It is about one-third the size of the right. The foramen ovale is patent. The mitral valve is represented by a tense sheet of endocardium without chordæ tendineæ or papillary muscles. Beneath this is a small endocardial-lined, blind pocket about 3 x 5 mm., representing the left ventricle from which there is no outlet.

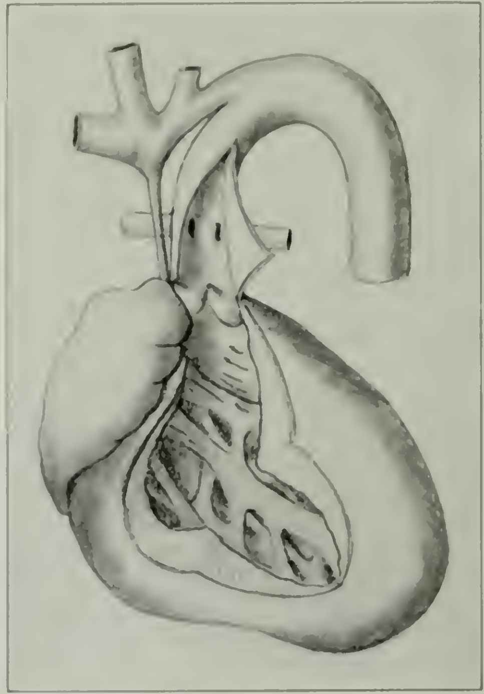


FIG. 1. Drawing of heart in case 1. Right ventricle and pulmonary artery opened.

This is a case of atresia of the whole left conus up to the aortic valves with resulting non-development and atrophy of the left ventricle and of the ascending aorta, the only function of the latter being to supply the coronary arteries with blood received through the ductus arteriosus.

Case 2. This case also was that of a male child that died on the fifth day, having lived exactly one hundred and twenty hours. He was well developed and nourished, and the history of the parents, as far as could be ascertained, was negative. On the afternoon of the third day while nursing he became suddenly dyspnœic, the respirations becoming very rapid and shallow. After this the whole surface of the body showed a dusky brown mottling. The temperature was 100.4. The urine showed albumin and a few pus cells. On the fourth day the dyspnœa and cyanosis were more pronounced. The capillary circulation of the finger tips was good and recessive on inspiration. Systolic murmurs were heard over the whole cardiac area but were not transmitted to the axilla or vessels of the neck. In the right infrascapular region was an area of dulness with increased voice sounds. On the sixth day the child died and the body was sectioned. All the tissues showed passive congestion and considerable edema. The lungs showed atelectasis, congestion, edema and some patches of pneumonia. The description of the heart is as follows: (1) The right auricle is quite large with the openings of the cavæ and coronary sinus in normal position. The septum ovale (primum) is absent, leaving a large irregular opening between the two auricles. (2) The right ventricle has a large chamber and thick walls (nearly twice as large as the left). The tricuspid valve is defective, irregularly formed and has vegetations on

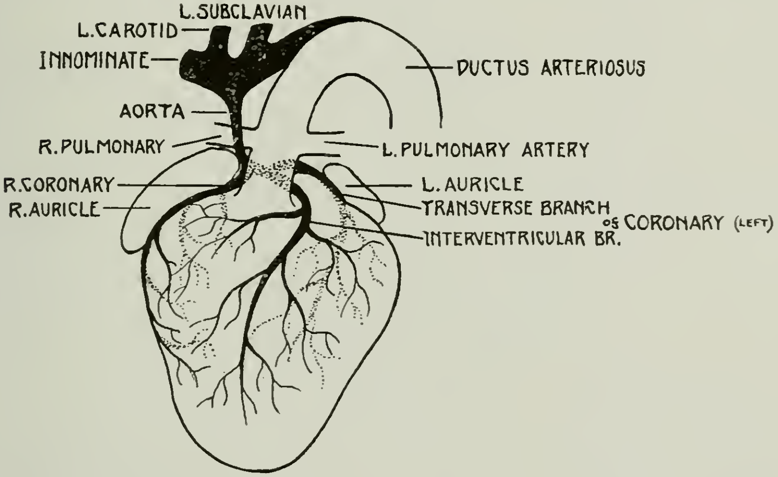


FIG. 2. Semi-diagrammatic drawing showing coronary arteries branching from the atrophic ascending aorta.

the cusps. The conus is large and points upwards to the right instead of to the left. There is a triangular shaped opening about 10 x 7 x 7 mm. in the bulbar region of the interventricular septum (Kieth's Bulbar Defect). The cusps of the pulmonary valve are covered with low vegetations. The pulmonary artery is large and lies slightly behind and well to the right of the aorta. After the right and left pulmonary branches are given off, the ductus arteriosus arches up and then turns downward to form the descending aorta. The only communication between the ductus and aorta is a small fibrous thread, one mm. in diameter, extending between its outer surface and that of the left carotid, which represents the obliterated isthmic portion of the aorta. (3) The left auricle and ventricle are only about half the size of the right chambers, the ventricle being in front of and twisted around the left ventricle as the latter is twisted around it normally. The mitral valve is deformed by fibrous adhesions and vegetations. The aortic valve is normal. The aorta emerges to the left and in front of the pulmonary artery and terminates in the innominate, left carotid and left subclavian branches. In short the left heart supplies the upper, while the right supplies the lower part of the body.

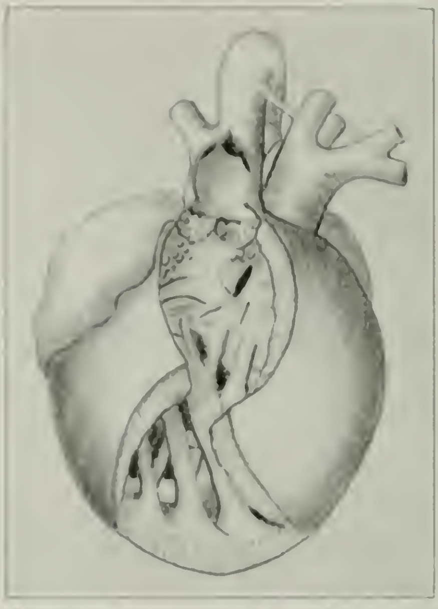


FIG. 3. Drawing of heart in case 2, showing right ventricle and pulmonary artery open, patent interventricular septum, vegetations on valves, atresic isthmus.

This is an extreme form of the second class of aortic stenoses, namely, stenosis—in this case atresia—in the isthmus or ductus region. There are two well-recognized forms of constriction in this region: (1) the fetal type, in which the stenosis is so great that the ductus must remain patent in order that life may continue; (2) the adult type, in which the constriction is not so great as to necessitate continued patency of the ductus. In this case it usually closes after birth. Later in life the constriction increases and necessitates the development of anastamoses between branches arising above and below the stenosis (internal mammaries, epigastric, scapular, intercostals, etc.).

Discussion:

Dr. Norris: I should like to ask in the first case of congenital heart disease whether there was any transposition of viscera or any other anomaly.

Dr. Fraser: No. There were no other anomalies in either case. They were both well-developed children.

TYPHOID LESIONS OF THE KIDNEY

ALEXANDER FRASER, M.D.

The lesion of the kidney usually found in typhoid fever consists of the degenerative changes common to all acute infections, or occasionally of embolic abscesses due to secondary infection. As far as I am aware, the specific typhoid lesion has not been described. Osler in his text-book on medicine mentions, without giving references, that Rayer, Wagner and others had encountered "small lymphomata which later may go on to suppuration," but evidently neither he nor they interpreted these as a specific reaction to the typhoid bacillus. Mallory, to whom I had shown sections of the cases about to be described, told me that he had seen an occasional small focus of endothelial leucocytic reaction, but never lesions so extensive or so typically developed as in this case.

The patient, a young sailor twenty-three years old at the time of his admission to St. Vincent's Hospital, had been ill eight days with a very toxic acute infection. He had roseolæ, some of which were hemorrhagic, a well-marked leucopenia with relative lymphocytosis, and gave several positive Widal reactions. The urine contained numerous cells which were interpreted as pus cells, but which judging from the results of an examination of the urine found in the bladder at autopsy I am satisfied were mononuclear phagocytes with ingested lymphocytes. The autopsy, which was performed about fourteen days from the onset of the first symptoms noticed, showed numerous typical typhoid lesions, mostly "cribriform" ulcers in the

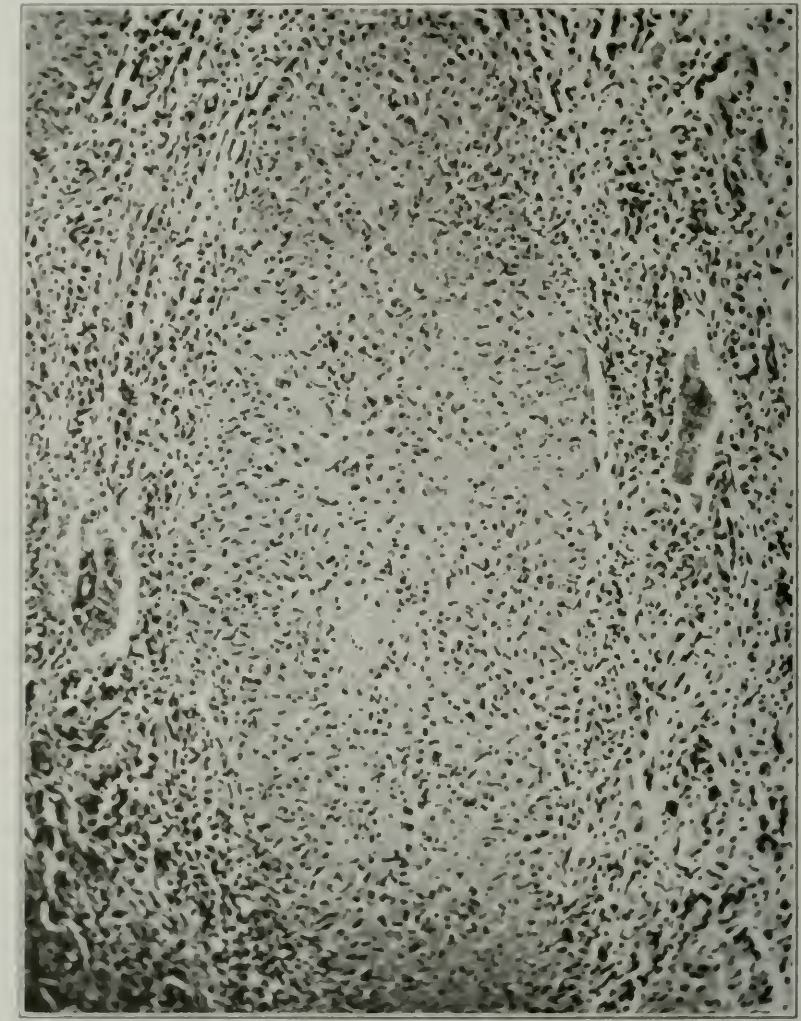


Fig. 1. Low power microphotograph showing typhoid lesion with central necrosis.

ileum and cæcum together with greatly enlarged, congested and occasionally hemorrhagic mesenteric lymph nodes. Microscopic examination confirmed the presence of true typhoid lesions in the intestine, lymph nodes spleen and bone marrow, but not in the liver. The kidneys presented a remarkable picture. They were both large and diffusely congested with numerous yellowish-white, elevated, rounded or oval areas with deep red borders scattered over the whole surface. Section showed these spots penetrating the whole of

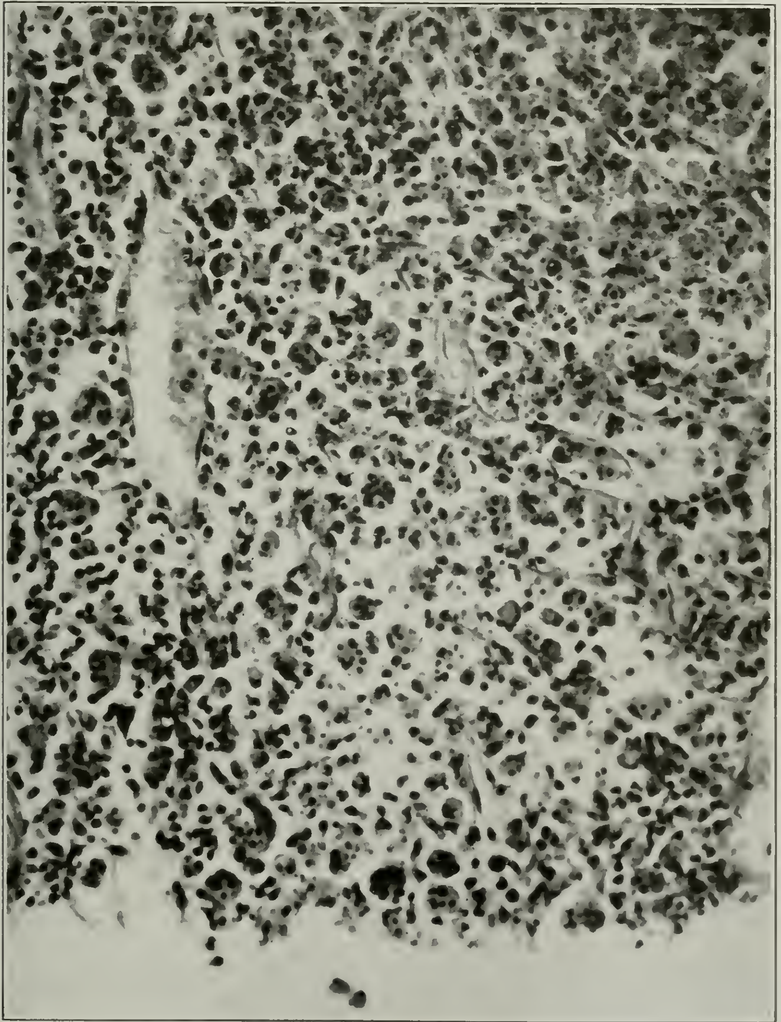


FIG. 2. High power microphotograph showing mononuclear phagocytes with ingested lymphocytes.

the parenchyma of both organs, presenting in the pyramids as long yellow streaks, extending over the pelvis and mucosal surface of the ureters and spreading out over the mucosa of the bladder. To the naked eye the picture suggested staphylococcus embolic abscesses, but microscopic examination shewed no polymorphonuclear leucocytes. The lesions consist of round, or elongated oval collections of large mononuclear phagocytes with extensive central necrosis (Fig. 1.) The well-preserved peripheral parts consist of a fair number of lymphocytes but mostly of large phagocytes containing lymphocytes and occasionally red blood cells in their cytoplasm, many of them showing ten to fifteen cells at a single focus (Fig. 2).

Such cases must be exceedingly rare or they have been overlooked in the routine examination of typhoid patients and interpreted as cases of secondary embolic abscesses. Histological examination of six museum specimens labeled "embolic nephritis" reveals one case exactly like this. So, too, examination of large numbers of sections from kidneys in typhoid fever, showing nothing macroscopically, convinces me that small isolated foci of true typhoid reaction are not at all infrequent. It is not improbable, too, that more careful microscopic examination of the urine in typhoid would show that not infrequently the "pus" cells found are mononuclears with ingested lymphocytes. A quick way of settling the question would be the use of the oxydase reaction.

HYPERPLASIA OF THE PARATHYROID GLANDS IN RICKETS

JOHN MINOR, M.D., AND A. M. PAPPENHEIMER, M.D.

(From the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York City)

Of late years considerable attention has been directed to structural changes in the parathyroid glands associated with diseases in which there is a disturbance of calcium metabolism.

Erdheim[1] had found in the rickets of rats a hyperplasia and hypertrophy of the parathyroid glands proportional to the intensity and the duration of rickets in the animals. He found also more numerous mitoses in the glands from rachitic than in those from normal animals. Although the reasons for these parathyroid changes are still to be explained, Erdheim regarded them as secondary to the rachitic lesions and not as the cause of them. In the parathyroids from human cases Erdheim was unable to differentiate histologically glands from rachitic and non-rachitic children.

Ritter[2] has recently studied the parathyroids from ten rachitic and fifteen non-rachitic children. None of his non-rachitic cases, however, fell within the usual age limits for the occurrence of rickets in children. He found that while in non-rachitic children in the first year the parathyroids consisted predominantly of clear cells belonging to the so-called Type I, in rachitic children they consisted almost entirely of dark smaller cells belonging to Type II, usually showed a marked increase in fibrous tissue, and marked hyperemia and edema. He also concluded from his study that no influence of the general state of nutrition of the child upon the histology of the parathyroid could be recognized.

The present study was made on the parathyroid glands of fourteen rachitic and eighteen non-rachitic children—routine autopsy material from the Nursery and Child's Hospital. Twenty-two separate glands were studied in the rachitic, nineteen in the non-rachitic cases.

In order to gain a general idea of the comparative size of glands from rachitic and non-rachitic infants, the sections were outlined at a constant magnification by the use of a projection apparatus. Allowing even for the gross inaccuracies of a method depending on the size of sections not known to be through the plane of greatest diameter of the gland, the area of the sections from the rachitic cases in almost every instance surpasses, and often greatly surpasses, that of the sections from the non-rachitic. Translated into volume, this certainly indicates a great excess of glandular tissue in the rachitic cases.

Our next problem then was to determine whether this increase in size were due to increase in the size of the individual cells, or to the multiplication of cells, or to some other factor. Choosing five glands from the rachitic and five from the non-rachitic series, from children of approximately the same age, careful measurements were made with the micrometer eye-piece of fifty cells and nuclei from each gland. The cells were chosen at random from all portions of the glands, only making sure to choose those as symmetrical in shape as possible. The results are shown in the table:

	Case No.	Age in Months	Nutrition	Cell Diameter in μ	Nucleus Diameter in μ
Non-rachitic	289	3	Poor	7.70	5.21
	299	6	Good	7.30	5.87
	325	$9\frac{1}{2}$	Fair	10.16	5.13
	320	$9\frac{1}{2}$	Good	10.20	5.83
	321 (II)	12	Fair	7.14	5.39
Rachitic	361	5	Emaciated	10.09	5.24
	333 (II)	8	Good	8.41	5.26
	334	9	Emaciated	7.51	5.10
	375	10	Good	9.30	4.92
	335	12	Good	10.31	6.23

It will be seen that there was found no constant difference in the size of either cells or nuclei in rachitic as contrasted with non-rachitic cases. Neither was there shown any constant relation of the size of cell or nucleus to the nutritional state of the child. Since the histologic study showed no increase in connective tissue, no edema and no difference in vascularity or congestion, we felt justified in concluding that the increase in size of the glands in rachitic cases is due to multiplication of cells.

A brief résumé of the histology of the parathyroid gland is as follows: There are three general types of cell arrangement—in compact masses, as cords of cells separated by blood vessels and connective tissue septa, and a less frequent form showing a lobular structure. There are also three types of cell found: I, clear, vegetable-like cells with unstained cytoplasm, large vesicular nuclei and clear cell outlines; II, rose-red cells with finely granular cytoplasm, small dark nuclei and indefinite cell outlines; III, Welch's oxyphile cells, which last are rarely found before the tenth year.

Comparative histologic study of the twenty-two glands from rachitic and nineteen from non-rachitic cases revealed no constant differentiating features. There was an increase in connective tissue in the glands in only one rachitic case, and this increase was only slight. There was no greater vascularity or congestion in rachitic than in non-rachitic cases, and no evidences of edema were found.

In all our sections, the clear cell belonging to Type I predominated markedly, and as constantly in rachitic as in non-rachitic cases. The other cells present belonged to Type II and showed no constant arrangement with regard to blood vessels. No mitoses were found; this, however, could easily be due to lateness of fixation.

Our conclusions from this study, then, are:

1. That there is a very definite increase in the size of the parathyroid gland in cases of human rickets, and that this increase in size is due to multiplication of cells, not to an hypertrophy of individual cells or increase in supporting structures.

2. That the parathyroid glands in children within the first eighteen months of life consist predominantly of clear cells belonging to Type I.

3. That in human rickets there is no constant or characteristic change in the cell type, and the clear cells still remain markedly predominant.

4. That in our cases there was no increase in supporting tissues in the parathyroid gland in rickets, and no increase in vascular supply, or evidence of congestion not found equally in non-rachitic cases.

5. That the state of nutrition of the child had no bearing on the size either of the gland as a whole or of the individual elements.

References

1. Erdheim: Rachitis und Epithelkörperchen Math.-Naturwiss. Kl. d. Kais. Akad. d. Wiss., 1914, xv.

2. Ritter, Carl: Ueber Epithelkörperchenbefunde bei Rachitis und andere Knochenerkrankungen, *Frankfurter Ztschr. f. Path.*, 1920, xxiv, no. 1.

Discussion:

Dr. Jobling: Definite conclusions cannot be drawn from this study by Drs. Minor and Pappenheimer, as the glands were not weighed and measured at the time they were removed, but the results are very suggestive.

Dr. Pappenheimer: There is an apparent paradox in the relation of the parathyroids to calcification, which has not been explained. It is generally known from the work of Erdheim and Toyofuko that complete destruction of the parathyroid in rats is followed by a failure of the dentine to take up calcium and also by a lack of calcium deposition in the callus of experimentally produced fractures. Identical changes, as regards the failure of calcium deposition, occur in rickets, but associated with a hyperplasia of the parathyroid. One can of course theorize about the explanation of this seeming discrepancy, but there is as yet no real explanation.

PRIMARY BONE TUMORS

Their Classification with Special Reference to Benign Giant-cell Tumor

H. S. MARTLAND, M.D.

(From the Pathological Department of the City Hospital, Newark, N. J.)

For a number of years I have noted a considerable confusion and lack of clear thought among surgeons and pathologists as regards the diagnosis, treatment and prognosis of the primary tumors of the long pipe bones belonging to the so-called sarcoma group.

It is rather unfortunate that even at the present time many able and even noted surgeons are extensively sacrificing limbs for tumors which have been known to be distinctly benign in character.

It is for this reason that I will attempt to summarize some of my experiences encountered in this type of tumors. I have tried to do this in as practical a way as possible, consequently much scientific data will obviously escape recognition in this discussion.

The primary mesenchymal tumors of bone may be roughly classified as follows:

TABLE I

Classification of Primary Tumors of Bone

Primary Mesenchymal Tumors of Bone

Fibroblastoma (fibroblast).
- *Benign:* Fibroma, and border-line fibrosarcoma (unusual).
- *Malignant:* Fibrosarcoma (see osteogenic sarcoma).

Myxoblastoma (myxoblast).
- *Benign:* Myxoma, myxofibroma, myxolipoma and myxochondroma.
- *Malignant:* Myxosarcoma, myxochondrosarcoma and osteomyxochondroma.

Chondroblastoma (chondroblast).
- *Benign:* Chondroma, ecchondrosis, chondromyxoma and osteochondroma. Multiple congenital enchondromata.
- *Malignant:* Chondrosarcoma, osteochondrosarcoma, etc.

Osteoblastoma (osteoblast).
- *Benign:* Osteoma, osteophytes, exostosis, endostosis, osteofibroma, etc.
- *Malignant:* Osteogenic sarcoma.

Endothelioblastoma (blood-vessel endothelioblast).
- *Benign:* None.
- *Malignant:* Endothelial myelomas and multiple hemangioendothelioma.

Myeloma (type cell unknown).
- *Benign:* None.
- *Malignant:* Multiple myeloma (Kahler's disease).

Benign Giant Cell Tumor.
- *Benign:* Single and multiple forms of disease (see ostitis fibrosa).
- *Malignant:* None.

If we examine Table I, it will be readily seen that most of the tumors group themselves into benign and malignant forms. Most of the benign forms, though not all of them, can as a rule be easily diagnosed by their history, location, age incidence, clinical appearance and X-ray examination, and therefore offer little confusion either to surgeons or pathologists.

Furthermore, the malignant forms, if studied more in detail, will dwindle down to a few important types. For example, fibrosarcoma would be a rare bone tumor if we interpret tumors belonging to this class as a fibrocellular variety of osteogenic sarcoma. In a like manner, myxosarcoma, myxochondrosarcoma, chondrosarcoma, etc., while they do occur as pure forms which metastasize, are nevertheless most often encountered as metaplastic areas in osteogenic sarcoma.

The confusing primary tumors of the long pipe bones, when a question of malignancy arises, usually exclude all but the following: osteogenic sarcoma, endothelioma, multiple myeloma and benign giant-cell tumor.

My experience has been that it is impossible, especially in central varieties of these tumors, to diagnose many of them from their age incidence, location of tumor or X-ray examination, but that an exploratory incision with histological examination of the tissue removed is necessary.

OSTEOGENIC SARCOMA

Of the many anatomical varieties of this tumor described in the literature, for teaching purposes I have adopted the simple classification of Ewing as the best, namely, fibrocellular and chiefly periosteal; telangiectatic, soft and richly permeated with blood-vessels and sinuses (bone aneurysm), involving marrow, shaft and periosteum; and sclerosing, a very hard osteoblastic growth, involving marrow, shaft and periosteum, and to a slight extent less malignant than the other two forms.

It has been found that practically all these growths sooner or later involve the periosteum, making a classification as periosteal sarcoma justifiable in a large majority of the cases. A central sarcoma without involvement of the periosteum I have never seen, and this is interesting, since Bloodgood has recently stated, "I would welcome an opportunity to study a solid central sarcoma in which there is no periosteal growth."

The important facts in osteogenic sarcoma are summarized in Table II.

TABLE II

SUMMARY OF IMPORTANT DATA IN OSTEOGENIC SARCOMA

PATHOLOGY:

Anatomical varieties	*Location*
1. Fibrocellular	Chiefly periosteal
2. Telangiectatic	Marrow, shaft and periosteum
3. Sclerosing	Marrow, shaft and periosteum
4. Capsular	
5. Parosteal	

HISTOLOGY:

Type cell: spindle, round and tumor giant cells.

Production of new bone.

Hyperchromatic nuclei and tumor mitoses.

CAUSE OF DEATH:

Early lung metastases.

AGE INCIDENCE:

Fifteen to seventy years. Cases few before fifteenth or twentieth year.

TREATMENT:

Radical Operation and treatment of any kind almost hopeless. Bloodgood's series showing less than 4 per cent. cures after radical operation and early diagnosis.

Radium supposed to be of little or no benefit (see Ewing's discussion).

ENDOTHELIOMA OF BONE

True primary endothelioma of bone has always been questioned by many pathologists, because of the close histological resemblance of the growth to metastasizing adrenal tumors, tumors of the thyroid, prostate, etc.

I believe that it does occur rather frequently as a single tumor. Rare multiple forms have been described, notably a case of multiple hæmangioendothelioma reported by Symmers, which clinically simulated multiple myeloma.

The importance of this type of bone tumor has recently been emphasized by Ewing, who a few months ago presented to this Society several cases of, I believe, undoubted primary endothelioma of bone, the cases being clear cut enough to form a distinct clinical and pathological entity in bone tumors. This remarkable contribution to the pathology of bone tumors, sharply identifying a type of tumor frequently submerged under the name of round-cell sarcoma, and often mistaken by pathologists for osteogenic sarcoma, is of especial importance, since the malignancy of this tumor is very much less than that of osteogenic sarcoma, persistent X-ray or radium treatment checking and apparently curing the lesion.

TABLE III

SUMMARY OF SALIENT POINTS IN ENDOTHELIOMA OF BONE

PATHOLOGY:

Anatomical varieties

1. *Single tumor:*

(*a*) Circumscribed, large bulky growths, arising in marrow or endosteum and early perforating shaft and developing externally.

(*b*) Smaller growths, many occurring in middle of shaft, and submerged in the diagnosis of round-cell sarcoma, periosteal sarcoma, etc. (Ewing's endothelial myeloma).

2. *Multiple Tumors*—

(*a*) Multiple hemangioendothelioma (Symmers), clinically resembling multiple myeloma.

HISTOLOGY:

1. *Single Tumor:*

Type cell is a round or oval shaped cell with clear cytoplasm and vesicular nucleus. Usually arranged in alveolar formation with little or no intercellular substance. Some portions of the tumor showing origin from blood-vessel endothelium. There is absence of new bone formation, but bone absorption is common

2. *Multiple Tumors.*

In Symmers's case the histological picture of hemangioendothelioma or angioma was very evident.

CLINICAL COURSE:

The single tumors are not nearly so malignant as osteogenic sarcoma and perhaps amenable to X-ray and radium treatment. Ewing states that tumors rapidly melt under radium but recur unless treatment is persistent.

MULTIPLE MYELOMA

This is most easily diagnosed by the X-ray examination showing multiple bone tumors, which demonstrates the importance of raying the skeleton in many bone tumor cases. The X-rays being distinguished from multiple metastasizing carcinoma by its predilection for bones with red-marrow and the absence of a motheaten appearance.

In a tumor in which the type cell is unknown, and has been described as a myelocyte, lymphocyte, plasmocyte or erythroblast, it is quite possible that with so great a variation in histological structure the explanation may be that we are dealing with an undifferentiated metrocyte, somewhat similar to the explanation suggested by Symmers in the disease "Leukanæmia" (a combination of myelogenous leukæmia and pernicious anæmia).

Multiple myeloma is a rare disease occurring in individuals over thirty-five years of age, oftenest in men, and pursuing a rapidly fatal course. It is characterized by foci of growth arising in different parts of the marrow system at approximately the same time involving bones with red-marrow, as vertebræ, sternum, ribs, skull, scapulæ and ilium. Spontaneous fractures are common. Bence-Jones albumose is frequently found in the urine.

It occurs in two anatomical varieties, the ordinary form or Kahler's disease in which the lesions are confined to the bones, and a very rare or extra-medullary form in which the lesions may be present in other tissues.

Histologically the type cell has been identified as either unknown, an adult or embryonal myelocyte, a lymphocyte, a plasma cell, or in rare instances as an erythroblast.

Treatment in this disease is of no avail, except mechanical to relieve pressure symptoms.

BENIGN GIANT-CELL TUMOR

Benign giant-cell tumor, medullary giant-cell sarcoma, giant-cell sarcoma of the epulis type, medullary giant-cell tumor, chronic non-suppurative hemorrhagic osteomyelitis (Barrie), etc., has been recognized for many years by a few surgeons and pathologists as essentially a benign lesion of bone. This fact, however, is unfortunately not appreciated by most surgeons, in spite of all the literature written on the subject.

The tumors usually occur in the ends of the long bones, especially the upper end of the tibia. The majority occur in young people. A definite history of trauma is often obtained and seems to be an important etiological factor in the single lesions. Their growth is slow and duration of disease long. They recur after incomplete removal, *in loco*, but I have never seen one metastasize to distant parts.

X-ray examination shows an expansive, abrupt and circumscribed growth with preservation of the bony shell. Distention may be great.

In gross appearance the tumor is usually confined within the periosteum, definitely circumscribed, not infiltrating, and is easily removed from its bony shell. It is distinctly vascular, simulates young granulation tissue, is friable, soft, oozes and resembles red-currant jelly or fresh-cut liver.

Histological examination shows a stroma like young granulation tissue, ranging from very cellular, often hemorrhagic, areas to older, non-cellular portions in which the fibroblasts are arranged in whorls and resemble slightly spindle-cell sarcoma. Active mitoses and hyperchromatic nuclei are, however, not present. Giant cells of the foreign body endothelial type with glassy cytoplasm and many (25 to 80) vesicular nuclei are numerous, often forming the predominant picture.

It has been my good fortune to have had under observation with Dr. F. R. Haussling, attending surgeon to the City Hospital, a case of benign giant-cell tumor of the lower end of the tibia for a period of ten years, during which time the lesion has been curetted several times. During this time we have noticed, both from the X-ray examinations, the character of lesion at operation and the histological examination of the tissue, that the lesion has been changing in character from an original solid benign giant-cell tumor to an extensive, localized fibro-cystic disease of the tibia. The lower end of the tibia at the present time shows a very large multilocular cyst of the bone with an old fibrous wall containing only a few giant cells.

I have also had the opportunity of following with Dr. Haussling a very remarkable case of multiple giant-cell tumors for a period of six years. This case I reported before this Society in 1915. At the present time only four well-marked cases of this disease have appeared in American literature.

For several years the tumors in this case which were located in the right superior maxilla, both fibulæ, both clavicles, femurs and ribs were expansive, more or less solid tumors chiefly in the myeloid part of the bones and well confined within their bony shells. They showed the typical histological picture of benign giant-cell tumor.

During the last two years, even in lesions which had not been curetted, these tumors have been becoming cystic along with extensive fibrocystic disease of the surrounding bone. The gross appearance of one of the lesions at last operation was one of multiple cysts with fibrous walls, showing histologically dense fibroblastic tissue with scant foreign body giant cells.

I do not believe that any single lesion has been under such a long observation, since the tumor is either cured by surgical curettement, etc., or the limb sacrificed by some ill-informed surgeon.

The multiple lesions in their extreme form are so rare that it is doubtful if any case has been observed over such a period of time. The changing in the character of the gross appearance and microscopic picture of the lesions in both the single and multiple case during this time of observation is, in my opinion, extremely interesting.

From my observations in these two cases I am of the opinion that so-called benign giant-cell tumor is entirely an inflammatory process in the nature of exuberant granulation tissue, located mainly in the myeloid part of the bone, formed as an attempt to repair previous bone destruction, due to trauma in the single lesions and in the multiple ones to some unknown cause. I believe the disease is one phase or rather an exaggerated phase of *osteitis fibrosa cystica.*

It is interesting to note that very similar growths are occasionally seen in the tendon sheaths which have microscopic pictures closely resembling these giant-cell tumors of bone, namely, the so-called benign xanthic extra-periosteal tumors of the extremities.

My conception of so-called *osteitis fibrosa cystica* may be roughly summarized in Table IV.

TABLE IV

Summary of Important Data in Osteitis Fibrosa Cystica

Name of Disease: In my opinion no good, permanent name has been suggested so far. Metaplastic osteomalacia is worth considering.

Pathology:

Anatomical varieties

1. *Localized lesions* (localized osteitis fibrosa cystica).
2. *Generalized lesions* (generalized osteitis fibrosa cystica of von Recklinghausen).

Location

Practically always in diaphysis and never invades epiphysis. Slow growth and moves up diaphysis. Most common in proximal end of shaft

Etiology

In single lesion trauma seems to be an important exciting factor. In generalized type of disease the cause is unknown, may be bacterial, nutritional or endocrinal. Usually appears before thirtieth year.

Sequence of Lesions

1. Destruction and absorption of bone (usually medullary in cancellous bone).
2. Granulation tissue formed in effort of repair: producing picture of young granulation tissue with hemorrhage, bone absorption and numerous foreign body endothelial giant cells.
3. Replacement by a less cellular fibroblastic tissue, a medullary fibrosis: producing a picture simulating spindle-cell sarcoma.
4. The lesion at this stage may progress in any of the following ways:
    - (*a*) Subside, due to softening of fibrous tissue, with formation of single or multiple bone cysts lined by a fibrous wall, the cyst fluid eventually becoming serous and often clear.
    - (*b*) Progress as a solid giant-cell tumor with or without cyst formation and finally heal or become bone cyst.
    - (*c*) Progress rapidly as a benign solid giant-cell tumor of local clinical malignancy with considerable destruction of bone.

TREATMENT: Radium or surgical curetting with crushing of diseased wall. The success of surgical treatment in our opinion has been due chiefly to *closure without drainage*, thus avoiding sepsis.

SUMMARY OF CASES REPORTED

CASE 1. Single, solid benign giant-cell tumor of lower end of tibia, changing in a period of ten years into a single multilocular bone cyst.

A. L. Male. Italian. Present age thirty-eight years. Barber.

Family History: Negative

Past History: Chancre when eighteen years of age.

Present History:

1907. Twisted right ankle while playing ball.
In plaster 3 weeks.
Syphilitic treatment for 3 months.
Plaster for 2 months.
Lower end of tibia curetted and discharged cured.

1908. Swelling and pain has returned.
Lower end of tibia curetted, diagnosis osteomyelitis.
Sinus persisted.

1910. Fell and injured ankle

Admitted to City Hospital.
Lower end of tibia curetted and diagnosis of solid benign giant-cell tumor made.
1911. Tibia curetted 4 times for recurrence.
1915. Tibia curetted for recurrence. The original tumor is no longer composed of granulation tissue, but consists of several cystic cavities filled with serous fluid.
1921. Patient in good physical condition. Has been able to work as barber all this time. X-ray examination shows a multilocular communicating cyst involving lower third of tibia.

CASE 2. Multiple, solid, expansive benign giant-cell tumors, changing in a period of six years into generalized fibrocystic disease of long bones.
T. K. Female. White. Present age thirty-one years. Married.

Family History: Negative.
Past History: Venereal diseases denied. Four normal births, one miscarriage.
1914. Noticed lump in inner angle of right eye.
Fell and fractured right femur above knee, which united with fair result.
Noticed tumor mass on anterior surface of left tibia.
Admitted to hospital complaining of weakness and pain in bones.
1st operation: tibial tumor curetted, microscopical diagnosis benign giant-cell tumor.
2d operation: tumors in maxilla, both fibulæ, both clavicles and rib curetted. Gross appearance of tumors that of pale granulation tissue, microscopical diagnosis benign giant-cell tumor.
3d operation: right elbow curetted.
1916. *4th operation:* left femur curetted.
1917. *5th operation:* right tibia curetted.
6th operation: clavicle curetted.
1919. *7th operation:* both tibiæ and left clavicle curetted.
8th operation: left femur curetted.
9th operation: finger curetted.
1920. *10th operation:* left femur curetted.
11th operation: left femur curetted.
1921. *12th operation:* left tibia curetted.

At all operations the wound was closed by primary suture without drains, this we regarded as a very important factor in preventing sepsis. The present physical condition of the patient is fair considering her long stay in hospital. She has a moderate secondary anæmia. Her blood chemistry is normal for nitrogenous waste retention, her calcium metabolism, however, has never been determined. The tumor masses in the last few years are distinctly cystic at operation and histological examination shows scant or no giant-cells present but old, dense fibroblastic cyst walls. The indication for operation has been pain. Many of the lesions have disappeared without surgical treatment but the surrounding bone shows extensive fibrocystic disease.

Of the American literature on bone tumors, especially giant-cell tumors, I have been greatly helped in my observations by the numerous writings of Bloodgood, Ewing, Barrie, Symmers and Meyerding.

Discussion.

DR. MOSCHCOWITZ. In twenty years' experience I have never seen a patient with a giant-cell sarcoma of the bone come to autopsy. I should like to ask those here if they have had the same experience.

DR. SYMMERS: What part of the bone do you mean?

DR. MOSCHCOWITZ. Any giant-cell sarcoma.

DR. EWING. I think Dr. Martland has given us a great deal of valuable information. I wish he could find time to carry it around to the places where it would do most good. Although the general statements which he mentioned have been known since 1852, the information needs to be spread broadcast in this country. At a recent meeting in this city of prominent surgeons about thirty were present, who were presented with evidence such as has been given to-night of a giant-celled sarcoma in the tibia with all the features and histology described, and they were asked to state what they would do. Twelve of the thirty would amputate. I think this is a deplorable state of affairs when the information is as clear as it is of the benign nature of this disease. The difficulty is not with these characteristic growths in which a large portion of the tumor is made up of giant cells, but in the variants of this disease. I have found quite a few tumors which are in all respects like those described, but in which the giant cells are scattered and the remaining tumor tissue is quite cellular and verging toward the ordinary malignant looking spindle-cell sarcoma. I am unable to come to a conclusion as to whether there are two diseases here which you cannot distinguish histologically and clinically, or by the X-ray, or whether this ordinary simple benign giant-cell tumor may in different cases become a clinically malignant, possibly metastasizing tumor. I am unable to decide what its relations are to the malignant cases of true osteogenic sarcoma. In cutting the capsules of these tumors I find varying degrees of bone formation and bone absorption, and if one sees only small sections, it is very difficult to distinguish the process from malignant osteogenic sarcoma, so I think it is better not to cut into these tumors and attempt to make a diagnosis on a small piece of tissue. One ought to have all the data in the case, including the X-ray. I have been looking for many years for an undoubted case of giant-cell sarcoma of the bone of the epulis type which had killed with metastases in the lungs. I have been unable to find such a case.

In regard to the treatment of these cases, which is really what the pathologist has to decide, my position is that none of these tumors should be cut into. You may not get a diagnosis. That so often happens in my experience that I prefer to rest the diagnosis on the clinical history, the age of the patient, the X-ray findings, and the general physical condition of the patient and the tumor. I agree with Dr. Martland that you cannot make a positive diagnosis in all these cases, but an incision does not always do it. I know many cases that have lost their limbs, and several that have lost their lives, from infection from bone cysts after exploratory incision and curettage. Many of them do badly, and Dr. Martland's patient is very fortunate indeed to have escaped infection in so many operations. Another reason for reaching this decision is that the benign tumors of this sort respond very well to treatment by physical agents, X-ray and radium. So also do the myelomas. In the malignant osteogenic sarcoma no method of treatment is satisfactory or successful, yet prolonged X-ray and radium treatment of osteogenic sarcomas in at least two cases has caused a complete disappearance of the local tumors, and the patients have remained well for three and a half and four and a half years, respectively, so that I would like to see what thorough X-ray treatment would do with the malignant osteogenic sarcomas. It is however difficult to get an opportunity to carry this out, for the patient will sooner or later fall into the hands of some surgeon who will cut the leg off. I have not been able to get a fair test of these tumors, but I am optimistic enough to say that if the limb could be immobilized and thorough X-ray or radium treatment be given over long periods the result might very likely be better in a series of cases than it is at present with amputation.

DR. MARTLAND: In reference to Dr. Moschcowitz's question. I do not believe that benign giant-cell sarcoma as I have described it ever does metastasize. I know there are a few cases on record in which it is claimed that the stroma has undergone so-called sarcomatous proliferation, but this has been very rare in giant-cell tumors, and I think those tumors which have metastasized have been the so-called periosteal or osteogenic sarcomas, in which you get a number of foreign-body giant cells, but you also get true tumor giant cells.

I agree with Dr. Ewing that some of the most eminent surgeons, who have had the best experience in bone sarcoma, seem to have no idea at all of what they are dealing with pathologically, and it is unfortunate that in the large cities we see extensive sacrifices of limbs which are absolutely unwarranted.

PRIMARY SPINDLE CELL SARCOMA OF THE LIVER ASSOCIATED WITH CIRRHOSIS

MORTON RYDER, M.D.

(From the Pathological Laboratories, Bellevue Hospital, Dr. Douglas Symmers, Director, New York)

The reported cases of primary sarcoma of the liver have been collated by different authors, the latest collection being that of

Marx in 1904—57 cases. Marx analyzed many of these cases only to condemn them. He accepts the majority as sarcomatous, but thinks that the evidence of their origin in the liver is unsatisfactory. Some cases were attended by smaller tumors in other organs, such as the adrenal or the periosteum of the vertebræ that Marx considers may have represented primary growths. Others were incompletely investigated post mortem or lacked autopsies altogether, the diagnosis being based on operative findings. Marx concludes, however, that when all these cases are excluded there remain a considerable number of undoubted primary sarcomata of the liver. Others have still further reduced the number of unchallenged cases by questioning the sarcomatous nature of many of the growths. Ewing emphasizes the danger of classifying growths with an alveolar structure as of connective tissue origin, and points out the resemblance of some of the tumors reported as angiosarcomata to atypical carcinomata. The rarity of cases acceptable to all makes it a duty to report the following, in which the diagnosis of sarcoma appears to be unquestionable, and in which there is no reasonable doubt that the growth had its origin in the liver.

The patient was a laborer, aged forty-seven, born in this country. The family history was uncertain; he denied venereal disease and the use of alcohol and tobacco. He professed to have had no severe illnesses until fourteen months before his death, when he suffered from an acute abdominal attack with pain in the right upper quadrant. He did not know whether he was jaundiced at that time. A diagnosis of gall stones was made and at operation a fistula was made from the gall-bladder to the abdominal wall; this fistula remained open until death. He did not know whether gall stones were found. He returned to work and remained well until February, 1921, when his legs and scrotum commenced to swell He was admitted to Bellevue Hospital on the service of Dr. Charles Nammack on February 16, 1921, and died eleven days later. During his stay in the hospital the patient was intensely jaundiced and moderately emaciated; mentally he was dull, not being aware of either the jaundice or the emaciation.

There were physical signs of pneumonia over both lower lobes. Examination of the heart was negative. In the epigastrium and right hypochondriac region there was felt a hard, nodular mass which corresponded in position to the liver and descended with inspiration. There was a ventral hernia at the site of a healed upper right rectus incision; at the upper end of the scar there was an open sinus discharging mucoid material. The scrotum and both lower extremities were moderately edematous. During his stay in the hospital he had a temperature range of 98° to 100°, pulse 100 to 120, respiration 20 to 24. The leucocytic count was 10,200 with 84 per cent. polymorphonuclears; red cell count, 4,000,000. The urine was negative except for the presence of bile. A provisional diagnosis was made of carcinoma of the gall-bladder with extension to the liver. Pneumonia was apparently the immediate cause of death.

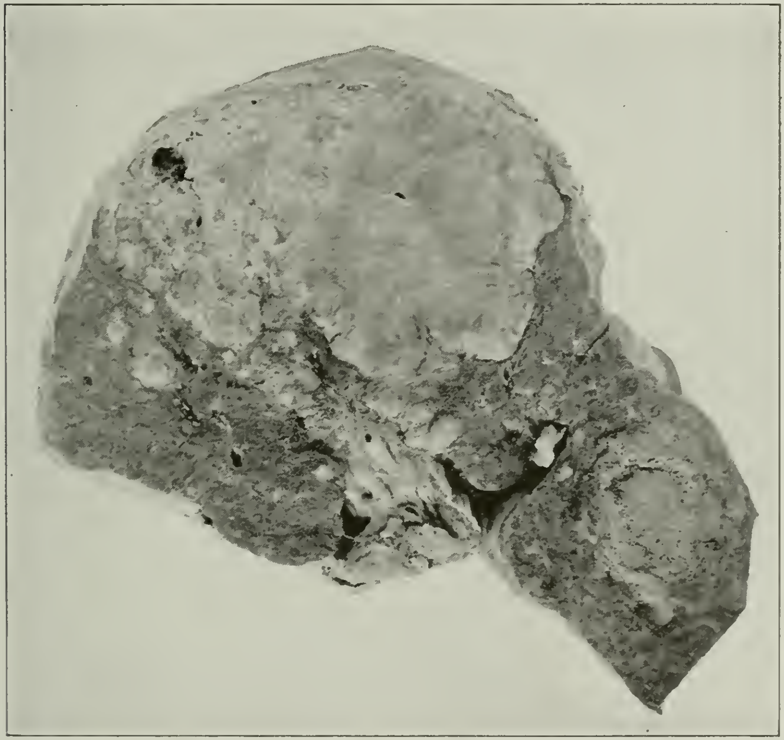


FIG. 1. Transverse section of liver through longest diameter.

Autopsy: The body was considerably emaciated, the abdomen slightly scaphoid. There was a moderate, soft, pitting edema of the lower extremities, scrotum and posterior body wall. The scleræ, skin and all the body tissues were intensely and uniformly icteric. There were large purpuric spots on the dorsum of both wrists and about the knees. The scar of the right rectus incision was recently healed at the upper extremity where the sinus had opened. The firm, nodular mass described could be felt two inches below in the xiphoid and just at the costal margin in the right mammary line.

The peritoneal cavity contained about 300 c.c. of thin, reddish-brown fluid. The entire visceral and parietal peritoneum was studded with slightly elevated, rounded, grayish-white nodules, measuring 1 to 2 cm. in diameter. The omentum was adherent to the cæcum.

The liver was about normal in size but very firm and tough. The liver substance was broken up by trabeculæ of white fibrous tissue distinctly seen on section, between which bulged out little nodules of brownish liver tissue. The surface was nodular, apparently from the same cause, the nodules varying in size from one to several millimeters. In the right lobe was a spherical mass, about 10 cm. in diameter, consisting of firm yellowish tissue mottled with areas of a salmon color, and everywhere streaked with barely visible grayish fibers. There were some portions which were lighter yellow and very soft, but the major portion was as firm as the surrounding liver tissue. This mass was rather sharply circumscribed, but had no definite capsule. It projected slightly from the upper surface of the liver to form an irregular, white, firm protuberance over the major portion

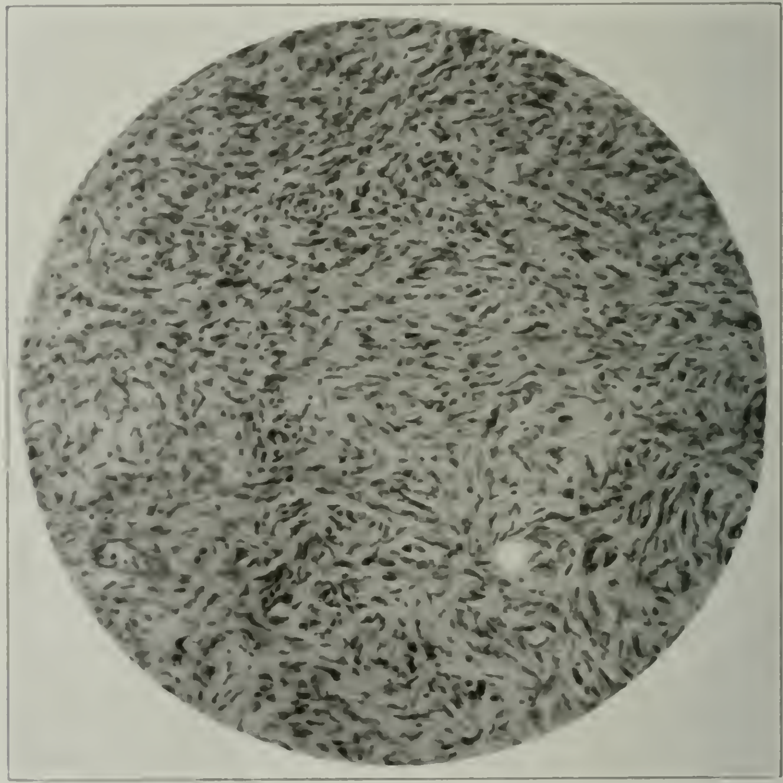


FIG. 2. High power photomicrograph of well preserved portion of growth.

of the right dome. Scattered throughout the liver were smaller nodules of similar tissue, some deeply imbedded, some on the surface. Those on the surface showed very slight umbilication and some showed central yellowish areas of softening. None of these masses was in close proximity to the gall-bladder, which was found in its normal site. The wall of the gall-bladder was thin and flexible, its mucosa apparently normal. From the fundus of the gall-bladder a sinus extended to the upper end of the abdominal scar, surrounded by dense white scar tissue. The duodenum and transverse colon were firmly adherent to the gall-bladder. They were opened before being dissected free and found to be normal. The œsophagus, stomach and small and large intestines were carefully explored, but no ulceration or tumor was found. Above the pancreas, from the head to the middle of the body, was a mass of discrete nodules of tumor tissue, suggesting replacement of lymph nodes. The pancreas was entirely separate from this mass and appeared

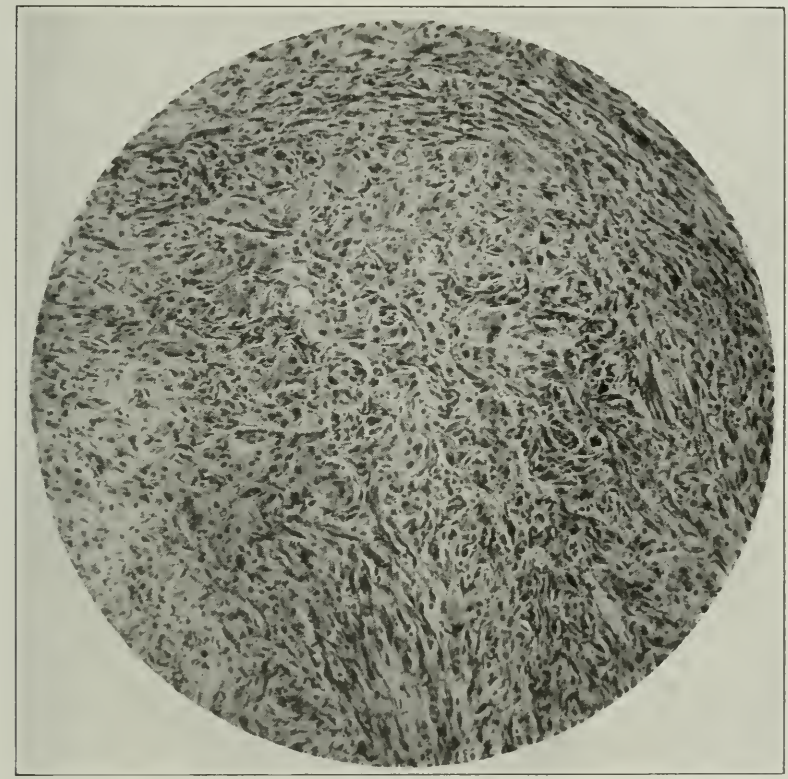


FIG. 3. Low power photomicrograph of margin of growth, showing islands of liver cells cut off completely by the tumor cells. These cells are loaded with yellow granular pigment.

to be normal. This chain of nodules extended to the portal structures, where they surrounded and pressed on the portal vein and common bile duct.

There was a similar mass of tumor tissue, measuring 1 x 3 x 4 cm., lying in the anterior mediastinum, just above the diaphragm. Both pleural cavities were partially obliterated by adhesions; the right contained about 300 c.c. of thin, amber-colored fluid. The visceral pleura over both upper lobes was studded with nodules similar to those in the peritoneum. There were healed tuberculous scars in the pleura at both apices. Both lungs were congested and edematous throughout, and there was patchy consolidation in the left upper and lower and right lower lobes. There were no nodules of tumor tissue in the lungs. There was complete obliteration of the pericardial cavity by fibrous tissue.

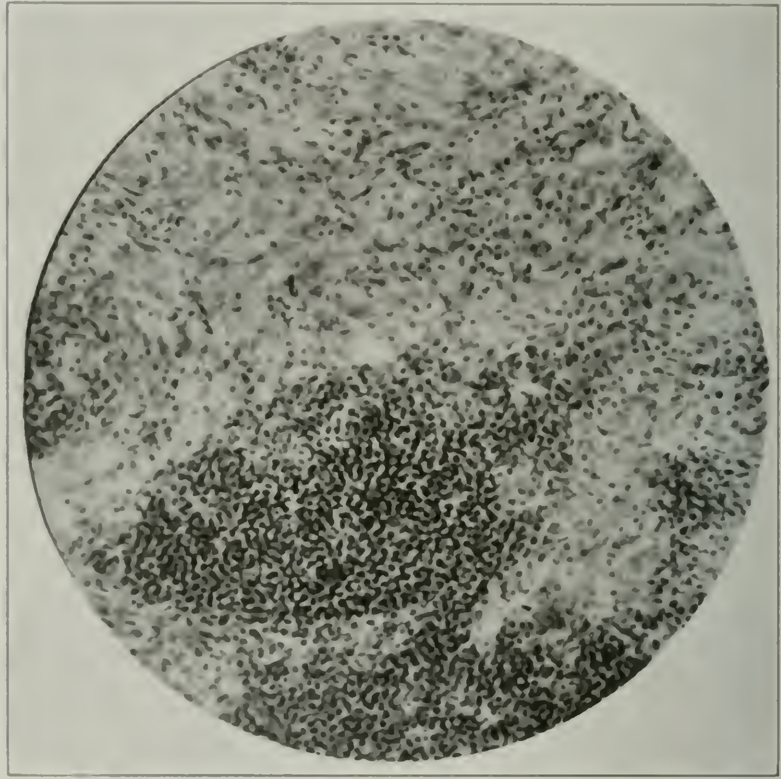


FIG. 4. Metastatic nodule in suprapancreatic lymph node.

The spleen was twice the normal size, soft and flabby, and, on section, raspberry-red in color with no focal changes.

The kidneys, adrenals, ureters, bladder, prostate, seminal vesicles, testes, epididymes, larynx, pharynx and thyroid were free from metastases and were essentially normal. No palpable enlargements were made out in the bony skeleton. Examination of the brain and spinal cord was not permitted.

Microscopic Examination: Microscopically, the well-preserved portions of the growth showed a uniform structure of large spindle cells lying in fasciculi, so that they were cut in all directions. They varied somewhat in size, but, in general, were large; the nuclei were oval, rich in chromatin and had no definite nucleoli. Mitotic figures were numerous. Occasionally there was a cell with two or three closely crowded nuclei, but these did not form a prominent feature of the growth. Blood vessels were rather scanty and they had no apparent influence on the structure or nutrition of the growth. There was no alveolar arrangement in any part of the tumor. Intercellular stroma was practically non-existent in some areas. In other places there was abundant hyaline transformation with a few scattered, elongated spindle cells. Other areas were frankly necrotic.

The liver tissue showed a high grade of cirrhosis, chiefly perilobular in type. There were wide bands of fibrous connective tissue with rich lymphocytic infiltration surrounding individual lobules or groups of lobules. In some places the connective tissue had grown between the cell cords. The liver cells toward the periphery of the lobules were loaded with pigment in yellowish-brown granules and the intercellular bile capillaries were distended with bile.

The tumor encroached directly on the liver tissue, without the intervention of a capsule, and tumor cells were seen growing into the liver lobules, enclosing finally small groups of liver cells or even individual ones loaded with granular pigment. There were numerous lymphocytes scattered through the growth, particularly in close proximity to the portal spaces.

The suprapancreatic nodes showed a pure spindle-cell growth with no necrosis or areas of hyalinization.

Of the tumors found, that in the liver clearly should rank as primary, and those in the lymph nodes, anterior mediastinum, pleura and peritoneum as metastatic.

Pure spindle-cell sarcomata of the liver were found only twice in a review of the literature, but many tumors were classed as spindle- and giant-cell, or spindle- and round-cell. The association with cirrhosis is interesting. Rolleston and Trevor collected seven cases, including one of their own, only one of which was a pure spindle-cell growth. In this the author found it impossible to say whether or not the cirrhosis antedated the tumor. In our case the cirrhosis is uniform throughout the organ and is of an advanced grade. In many of the nodules tumor cells are seen growing in the inflammatory tissue in the portal spaces, so that the possibility is suggested of a multiple origin of the growth secondary to the cirrhosis.

Addenda: Acting on a suggestion made during the discussion, preparations of the liver have been stained by the Levaditi method for spirochætes and by carbol-fuchsin for tubercle bacilli, but no organisms have been found.

The following brief notes of two cases resembling ours quite closely are appended:

1. From Arnold, In *Ziegler's Beitrage*, 1890, viii, 123. A man, fifty-three years old, for six months before his death had increasing jaundice, ascites and edema of the feet. He was in the hospital for one month. A hard nodular mass was felt in the epigastrium. Paracentesis was done twice, removing blood-tinged fluid. At autopsy, he presented intense jaundice and moderate ascites (the abdomen contained six liters of bloody fluid). There were pea-sized nodules throughout the omentum and mesentery, a few in the serosa of the intestine and a few in the pleura and bronchial nodes. The liver was much enlarged, coarsely granular and icteric. There was much interlobular connective tissue, sometimes enclosing several lobules, more marked near the tumor. In the right lobe was a tumor measuring 13 x 10 cm. and reaching the capsule; there were several smaller tumors in the vicinity and a beet-sized nodule at the base of the pericardium. Microscopically, the growth showed round, angular and spindle-shaped cells and a few giant cells. They grew around the blood vessels and seemed to spring from the adventitia. Arnold felt that the histogenesis was not certain, but that the sarcomatous nature of the tumor was undoubted.

2. From W. W. Ford, *Amer. Jour. Med. Sc.*, 1900, p. 413. A man, aged 59, with a markedly alcoholic history, died as a result of cerebral thrombosis. His abdomen had been increasing in size for some time. At autopsy, he presented no jaundice. The abdomen contained 4,000 c.c. of clear yellow ascitic fluid. The mesentery and omentum were filled with small nodules the size of a pea, white or reddish; similar nodules were scattered over the peritoneal surface of the abdominal muscles and diaphragm. The liver was small and showed an advanced grade of cirrhosis, principally intralobular. There was a tumor measuring 5 x 8 cm. in the right lobe. The center was soft, white and friable, the peripheral portions firm and grayish white. Microscopically, it consisted of round and spindle cells with central necrosis. The metastases were of the same structure with many blood vessels.

Discussion

Dr. Ewing: I should like to express my great interest in this case. I have never seen anything like it. I do not feel that there is any definite ground on which one can successfully attack the diagnosis. It is unique in my experience, and as far as I know, there is nothing exactly like it in the literature.

Dr. Norris: I have not had a very good look at the section. It was under low power, and I would not want to say anything about it. The question of these sarcomas of the liver is however occasionally very difficult to decide. I remember I reported the case of a woman before this Society six or seven years ago, in which Dr. Hermann M. Biggs made the clinical diagnosis of primary sarcoma of the liver. It was a very large liver, weighing two or three pounds, and at autopsy there was found an epithelioma just above the cardia of the esophagus. The sections of that tumor are strikingly like a sarcoma and I presented it, and received considerable credit and discredit for bringing it to the Society just for diagnosis. I suppose in that case, where there was a distinct primary tumor at the lower end of the esophagus, the only fair conclusion was to call it a carcinoma, but that tumor as I recollect was very vascular and had a tendency toward alveolar formation and distinct large spindle cells. This tumor to-night evidently has small spindle cells, and apparently has no resemblance to a carcinoma or an epithelioma. It seems to me with the hasty examination I have been able to give it that the diagnosis of primary sarcoma is the correct one.

Dr. Ewing: Did you consider the possibility that this might be a peculiar granuloma? There are a great many lymphocytes all through the tissue. The general behavior of this tumor seems to me not that of a sarcoma. The tumor is not very bulky. It seems to replace the liver rather than to cause a great increase in the bulk of the tissue. It invades the lymph nodes, which sarcomata do not do, as a rule, and it is not in the lungs. There is very extensive necrosis in the tumor, which suggests doubt as to its nature. I am not convinced that this is properly to be classed as a simple sarcoma. What is sarcoma anyway?

Dr. Norris: May I have another word? Although I hesitate to mention it, in all these rare tumors of the liver one must always think of melanoma, though it seems extraordinary to bring it up in reference to this case. Melanomas are so variable that a primary tumor might have been neglected or overlooked. I see no reason for thinking it is a melanoma, but I remember one case of a woman who had an eyeball tumor about six years ago. She had a melanoma, and an ovarian tumor with melanoma in it, with adrenal metastases.

Dr. Ryder: The presence of the lymphocytes was not overlooked. They were found in greatest numbers in the inflammatory tissue in the portal spaces, and we considered them part of the inflammatory process in the liver rather than an integral part of the tumor.

A REPLY TO DR. JOHANNES FIBIGER ON THE SUBJECT OF IRRITATION TUMORS

FRANCIS CARTER WOOD, M.D.

(*From Columbia University, Institute of Cancer Research*)

On December 8, 1920, at the request of Drs. Bullock and Curtis, I presented before this society a report of some experiments done in the Institute of Cancer Research on the artificial production of sarcoma of the liver in rats. That Dr. Fibiger received from the published account of these experiments the impression that Drs. Bullock and Curtis did not appreciate the importance of his work on *Spiroptera* cancer is evidenced by a letter received from him. Since he is displeased with their account it seems advisable to give to the society in his own words the corrections he thinks should be made in their statements:

DR. FRANCIS CARTER WOOD

Dear Sir. I have received the valuable paper of Bullock and Curtis: "The Experimental Production of Sarcoma of the Liver of Rats,"[1] and I beg you to accept my most hearty thanks for forwarding it to me.

I cannot, however, conceal that I have been highly surprised on seeing the incorrectness with which Bullock and Curtis have reported various particulars of some of my previous papers, and I shall therefore beg to address to you the following remarks, reserving, as a matter of course, my entering occasionally a public protest against the way of reporting used by Bullock and Curtis.

In the paper in question (p. 150) they write that "he (Fibiger) obtained 54 tumors (*Spiroptera carcinomata*) in the 134 animals which lived for 30 days or longer." In my paper: "Investigations on the *Spiroptera* Cancer III" (*Det. Kgl. Danske Videnskabernes Selskabs Biologiske Meddelelser,* 1918), p. 17, I distinctly wrote that "out of the 134 rats which lived in the space of time concerned, 18 were subjected to no sufficient microscopical examination or to none at all." Thus, it was impossible to include these 18 rats in the table showing the frequency of the *Spiroptera* carcinoma (p. 18). The 54 tumors, then, were not found among 134 rats, as reported by B. and C., but among 116 rats, and it cannot be known whether or not carcinomata would have developed in the remaining 18 rats.

When the authors write further: "In 8 of the 84 cases he (Fibiger) observed lung metastases," this statement, too, is wrong. Pages 25–26 in the paper quoted, the following passage will be found: "Altogether, in special examinations on metastasis formation, metastases have, thus, till now been found in 8 out of 33 rats, and in 2 of 3 white mice, mentioned above, in whose stomach *Spiroptera* cancer had developed." This permits of no misconception and it is beyond excuse when Bullock and Curtis are giving the number of the rats in which metastasizing carcinomata were found as being 8 out of 84, as my paper contains the statement: 8 out of 33, no special examination on metastasis formation having been performed in the remaining 51 cases.

But the errors of Bullock and Curtis still seem to culminate in the following passage (p. 152 of their paper). They write here: "Fibiger and Bang reported the development of 22 carcinomata and 2 carcinosarcomata in 26 (tar-painted) mice which lived six months or longer. Of these tumors, 6 metastasized in the axillary lymphnodes and 2 in the lungs, and 3 grew on transplantation. Thus so far a great amount of labor and a large number of animals have been required to produce a few tumors, most of which are not transplantable."

How the fact that malignant growths were produced in 24 out of 26 tar-painted mice can be characterized by Bullock and Curtis as a production of "a few tumors," must be completely inconceivable to any rational reader. But still worse is the next passage: "most of which are not transplantable." Page 23 of Fibiger's and Bang's paper quoted by the authors contains the following passage: "Attempts were made in 3 cases to transplant the developed carcinomata, but in 2 cases without success. In one case transplantation gave positive result." On pages 26–27 successful transplantation of a carcinosarcoma is reported, and on page 32, that transplantation experiment was effected with positive result in one case of tar carcinoma.

Transplantation experiments, thus, were made altogether in 5 cases, and in 3 of these with positive result, and it remains unknown whether or not the remaining 19 tumors (out of the 24) would have shown transplantability, transplantatation experiment being not performed in these cases.

To any reader this will be quite clear. Bullock and Curtis, thus, impossibly can have any idea as to the frequency of transplantable tar growths, and their report concerning the transplantability of these tumors is perfectly wrong and misleading.

A correct description of the transplantation experiments made by Fibiger and Bang rightly ought to have run as follows: "Fibiger and Bang have made transplantation experiments only with 5 tumors, out of which no less than 3 were transplantable." That this number must be considered very great is an obvious fact, because transplantation of keratinizing tumors, as commonly known, will frequently meet with great difficulties (see Fibiger, Investigations on the *Spiroptera* Cancer VI, page 16, *Det. Kgl. Danske Videnskabernes Selskabs Biologiske Meddelelser,* 1919). Nevertheless, transplantation turned out successful with 2 out of 4 keratinizing transplanted tar carcinomata.

And Bullock and Curtis, no doubt, then would have omitted the point 8 of their summary, in which they speak of the "sharp" contrast of the transplantability of the cysticercus sarcomata with the "few" transplantable growths reported by other investigators.

I may add that the authors do not even mention the successful transplantation experiment made by Yamagiwa in a case of tar sarcoma of the breast of a rabbit, quoted in the paper of Fibiger and Bang. I beg you to be sure that these remarks are impelled not only by my personal wish to have a correct report of my investigations, but besides, by a regard for you yourself and for your Institute. Previously (in the *Journal of Cancer Research*) I have pointed out some incorrectness of Bullock and Rohdenburg's report of my former investigations, and I should now prefer to avoid a repeated criticism, which certainly would not increase the respect rightly due to Bullock and Curtis'—in other respects—very valuable paper.

Seeing in the report of the discussion, held in the New York Pathological Society, the remarks of Dr. Rohdenburg on my slides (p. 173), "If you take some of his (Fibiger's) and put them beside ours without seeing the labels, I doubt whether you could tell which was which," I should be very grateful if you would kindly send me such slides, belonging to the experiments of Bullock and Rohdenburg, as are demonstrating the correctness of these words. Certainly, Dr. Rohdenburg has examined some microscopical preparations of mine, and I don't believe Dr. Rohdenburg should have made the mistake of saying or supposing that the changes found in my slides were all in every place meant to be carcinomatous. Several of these preparations only contain carcinomatous changes in a few distinct limited places of the slides. But according to the plates published in the *Journal of Cancer Research* changes of this kind have never been found in the experiments of Bullock and Rohdenburg.

Yours truly,
(signed) JOHANNES FIBIGER

Dr. Fibiger's erroneous impression is no doubt based somewhat upon a previous publication by Bullock and Rohdenburg,[2] which questioned, and quite justly, the proof of the malignancy of irritation hyperplasias when based on morphology alone. Since this paper was published, however, further experiments with *Spiroptera* and with tar have added convincing biological evidence that malignant tumors have been produced by these agents; yet despite this Murray and Woglom[3] in a recent paper still repeat the caution that morphology is not a sure criterion of malignancy. Bullock and Curtis gave full credit to the several investigators who had produced malignant tumors by means of irritants, and it is to be regretted that there was any misunderstanding of their appreciation of the very great significance of these results.

The experimental production of cancer by irritants unquestionably opens a new field in cancer research, comparable to the discovery of the transplantability of cancer, and it is unquestioned that Drs. Fibiger, Yamagiwa, and Ichikawa are the pioneers in the experimental production in animals of malignant irritation tumors.

But there are certain points raised in Dr. Fibiger's letter which are, in our opinion, the result of complete misunderstanding of the facts brought forward in our publication and require detailed discussion.

In reply to his criticism of Drs. Bullock and Curtis' treatment of his data dealing with the proportions of tumors and metastases, it should be explained that they treated his material exactly as they did their own. That is, the infested animals which survived to the cancer age were counted as negative unless there was known evidence that they were positive, even though they received only a macroscopic examination. In respect to their own data at least, it is certain that this is the fairer procedure. With the large amount of material handled in these experiments it would be humanly impossible to make a complete histological study of all the liver cysts in each animal autopsied. Therefore, reliance was placed chiefly on gross diagnosis confirmed in each case by microscopical examination. The parasite was removed from each cyst, and any cyst showing suspicious localized or diffuse thickening was preserved for microscopic study. A large proportion of the cysts which appeared negative macroscopically were discarded. A relatively small number, however, were retained and examined histologically in search of early sarcomatous changes. In this group a very few early sarcomata were found, but the proportion was small. Since malignant changes exist, before they can be recognized in the gross, as thickenings of the cyst wall, a few tumors were undoubtedly lost by discarding the animals in which no tumor or suspicious cyst could be recognized by the eye. However, since all the tumor-bearing animals and those with suspicious cysts were in the class examined, while the animals from which cysts were not examined appeared negative in the gross, it would be manifestly unfair to base the proportion of tumors only on the former highly selected group. We naturally suppose that other investigators examine microscopically every suspicious lesion and discard only such animals as they believe to be negative.

Even the complete microscopic examination of every cyst from every animal autopsied would be an imperfect test of susceptibility, for in the observed cases the duration of the period of irritation associated with early sarcomatous transformation varied by seven months. The number of animals dead from other causes during this period, *i.e.*, from seven to fifteen months after infestation, which were negative at autopsy, but which would have developed tumors had they lived longer, is probably large in proportion to the number in which there was a malignant change in a cyst wall visible only under the microscope. That is, were it possible to make the complete microscopic examination of every cyst the error of counting certain susceptible animals as immune would be reduced but not eliminated. This type of error is inherent not only in all studies of susceptibility to irritation tumors but in nearly all studies of susceptibility to any particular disease. It is rarely possible to be positive that every negative individual is immune.

The culminating error by which Drs. Bullock and Curtis seem to have particularly offended Dr. Fibiger is the following statement: "Thus, so far a great amount of labor and a large number of animals have been required to produce a few tumors, most of which are not transplantable." This sentence, which is a separate paragraph, refers, as "any rational reader" will note, to all the investigations on irritation tumors cited and has no particular reference to Dr. Fibiger's experiments. At the time the statement was made we knew of only seven such tumors which showed growth on transplantation. This number includes the temporary growth obtained by Clunet,[4] and also the "tar sarcoma" (myxofibrosarcoma mammae) of the rabbit produced by Professor Yamagiwa and his associates, to which latter tumor Dr. Fibiger refers in his letter. For the information regarding this transplantable tumor we were indebted to Fibiger and Bang[5] (page 8) who must have obtained their information from a letter to Dr. Fibiger from Professor Yamagiwa. There is no description of a myxofibrosarcoma mammæ in the paper[6] referred to by Fibiger and Bang. This tumor no doubt is the one described by Yamagiwa, Suzuki, and Murayama,[7] in a publication received since the paper of Drs. Bullock and Curtis went to press.

According to these authors the transplantation experiments resulted in a few small growths, none of them larger than a grain of rice, but some of these which were examined microscopically showed evidence of growth. Propagation beyond the first generation was apparently not undertaken.

We do not wish to overvalue the material developed by Drs. Bullock and Curtis in comparison with that employed by other investigators, but it should be stated that the liver sarcomata which arose in the walls of the *Cysticercus* cysts were not subject to the difficulties of transplantation which Fibiger admits in the transplantation of keratinizing tumors.

Of the 43 *Cysticercus* sarcomata tested by homoplastic transplantation, only 2 failed to grow progressively. Some of the grafts from 1 of these 2 tumors showed temporary growth, the largest reaching the size of a white bean. The rat bearing this primary tumor showed small metastic nodules in the omentum. In the second case which failed to grow progressively on transplantation the tumor was infected and abscesses were formed at the sites of inoculation. That is, homoplastic transplantation of *Cysticercus* sarcoma is successful in a high percentage of cases.

A simple method of determining the malignancy of irritation tumors has been demonstrated by experiments described in a valuable paper recently published by Murray and Woglom.[3] These authors relied chiefly on the progressive growth of autografts (artificial metastasis) as the criterion of malignancy. The vast majority of *Cysticercus* sarcomata perform their own autoplastic transplantation, as is evidenced by the very general occurrence of peritoneal metastases, and, hence, do not require homoplastic transplantation to establish their malignancy.

We have examined the microscopical preparations of *Spiroptera* cancer to which Dr. Fibiger refers in his letter. While in some areas these experimental tumors suggest a type of epithelioma which occurs in man, we would not feel justified in calling such lesions epithelioma merely because they show morphological resemblance to epidermoid cancers. They do not exhibit the unrestrained invasive growth that in itself is diagnostic of malignancy; rather, they are localized epithelial reactions which show in one or more small limited foci a suggestion of infiltrative growth associated often with some degeneration or keratinization of the epithelium. In our opinion at least, one of the lesions which Dr. Rohdenburg mentioned in the discussion referred to by Dr. Fibiger simulates epithelioma as closely as any of the nine preparations of Dr. Fibiger's which we have studied. This lesion was described and figured (Plate 14) in the paper by Drs. Bullock and Rohdenburg.[2] They believed that the morphological evidence obtained in their experiments and in the early experiments of Fibiger[3] and of Yamagiwa and Ichikawa[9] was insufficient for a diagnosis of malignancy when unsubstantiated by biological proof. As stated in the communication which Dr. Fibiger criticizes, and restated in the present paper, the malignant nature of some but not all the growths produced in response to irritation by *Spiroptera* and by tar has been demonstrated conclusively by metastasis formation and by transplantability. We agree with the statement of Murray and Woglom that "it would be hazardous and inadvisable to attempt to decide whether the new formations described by our predecessors are in every case rightly included in the malignant new growths or not. It is even probable that some of the tumors regarded as benign by them would, if tested by autoplastic transplantation, have given evidence of progressive independent growth."

It is impossible to judge how important a rôle the interpretation of the lesions plays in the varying proportion of tar cancers reported by different investigators. In comparing their own results with Tsutsui's,[10] Fibiger and Bang[5] suggest that their relatively larger number of tar cancers may have been due to a difference in the tar used or to a difference in the susceptibility of the Danish and Japanese mice. Each of these factors may be partly responsible. Bloch and Dreifuss[11] have recently reported the isolation from coal tar of the agent effective in the production of tar cancer. It is possible that the proportion of this ingredient varies in coal tar from different sources. That there is in rats a difference in the susceptibility to *Cysticercus* sarcoma of strains and even of families within the same strain is already indicated by the experiments which Drs. Bullock and Curtis are carrying on, in which 440 of these tumors have so far been produced. A difference in susceptibility seems to be the most probable explanation of Schmitt-Jensen's[12] failure to produce *Cysticercus* sarcomata of the rat liver by experiments which in all essential particulars duplicated those of Bullock and Curtis.

In conclusion it seems to us that the several experimental methods of producing malignant tumors are supplementary and that coöperation between the investigators would prove advantageous in the solution of the problems which have already presented themselves in connection with these irritation tumors.

References

1. Bullock and Curtis: *Proc. New York Path. Soc.*, 1920, N. S., xx, 149.
2. Bullock and Rohdenburg: *J. Cancer Res.*, 1918, iii, 227.
3. Murray and Woglom: *Seventh Sci. Report, Imperial Cancer Research Fund, London*, 1921, p. 29.
4. Clunet: *Researches expérimentales sur les tumeurs maligues, Paris*, 1910, p. 297.
5. Fibiger and Bang: *Det. Kgl. Danske Videnskabernes Selskabs Biologiske Meddelelser*, 1912, iii, 4.
6. Yamagiwa and Ichikawa: *Mitt. a. d. med. Fakult. d. k. Univ. Tokyo*, 1919, xxii, 1.
7. Yamagiwa, Suzuki and Murayamo: *Mitt. a. d. med. Fakult. d. k. Univ. Tokyo*, 1920, xxv, 189.
8. Fibiger: *Ztschr. f. Krebsforsch.*, 1914, xiv, 295.
9. Yamagiwa and Ichikawa: *Mitt. a. d. med. Fakult. d. k. Univ. Tokyo*, 1915–16, xv, 295–344; 1917, xvii, 19; *J. Cancer Res.*, 1918, iii, 1.
10. Tsutsui: *Gann*, 1918, xii, 17.
11. Bloch and Dreifuss: *Schweizer. med. Wchnschr.*, 1921, li, 1033.
12. Schmitt-Jensen: *Den Kgl. Veterinaerv g. Landbohjskole aarsskrift.*, 1921, p. 91.

Proceedings
of the
New York Pathological Society

New Series. Vol. XXI. OCTOBER-DECEMBER, 1921 Nos. 6-8

CONTENTS

Page

Active Immunity Against Experimental Pneumococcus Type 1 Pneumonia in Monkeys Following Intratracheal Injection of Vaccine. *Russell L. Cecil, M.D., and Gustave I. Steffen, Ph.D.* 132

Preliminary Report on the Nature of the Immunizing Antigen of Pneumococcus, Type 1. *William A. Perlzweig, Ph.D.* 133

The Skin Reaction in Bronchial Asthma and Allied Conditions. *Nils P. Larsen, M.D., Royce Paddock, M.D., and Harry L. Alexander, M.D.* 135

Two Cases of Human Actinomycosis. *Paul F. Russell, M.D.* 143

Endocrine Gland Studies, Including Goitre, in India. *Robert McCarrison, M.D.* 154

Tumors (3) of the Kidney Pelvis and of the Ureter. *P. W. Aschner,* M.D. 175

Aneurysm of the Hepatic Artery. *William Friedman, M.D.* 177

Calcification of the Pericardium. *A. Winkelstein, M.D.* 181

Multilocular Echinococcus of the Liver. Hydatid Echinococcus of the Spleen. *Leo Edelman, M.D.* 185

Teratoid Cyst of the Hypophysis. *J. H. Globus, M.D.* 188

A Contribution to the Pathology of Subacute Epidemic Encephalitis. *J. H. Globus, M.D., and I. Strauss, M.D.* 195

ACTIVE IMMUNITY AGAINST EXPERIMENTAL PNEUMOCOCCUS TYPE I PNEUMONIA IN MONKEYS FOLLOWING INTRATRACHEAL INJECTION OF VACCINE

RUSSELL L. CECIL, M.D., AND GUSTAV I. STEFFEN

In a recently published article, we have shown that three large doses of pneumococcus Type I vaccine injected subcutaneously at intervals of one week produce a complete immunity in monkeys against experimental pneumococcus Type I pneumonia. Furthermore, we showed that satisfactory immunity can be produced by several *small* doses of pneumococcus Type I vaccine if the injections were made intravenously.

We have recently studied the effect of pneumococcus Type I vaccine when injected directly into the trachea of monkeys. As in the previous experiments, three inoculations were made, separated from one another by intervals of one week. The skin over the neck of the monkeys was sterilized with tincture of iodine and the vaccine injected through the skin into the trachea by means of a hypodermic syringe. The doses used were 20, 40, and 60 billion, making a total of 120 billion of killed pneumococci. The volume of vaccine injected was, in every instance, one cubic centimeter. In these experiments, as in previous experiments with pneumococcus vaccine, the immunity of the monkeys was tested two or three weeks after the completion of vaccination. As in previous experiments, all monkeys were killed at the end of the period of observation, in order to determine the presence or absence of pneumonia.

The results of vaccination by the intratracheal route were entirely satisfactory. The three vaccinated monkeys remained perfectly well, while the control developed a mild but very definite pneumonia from which he recovered.

We are now attempting to vaccinate monkeys by spraying their throats with pneumococcus vaccine. This experiment however has not yet been completed.

The intratracheal administration of pneumococcus vaccine appears rational in view of the fact that pneumococcus infection usually takes place by this route. We have shown in previous articles that immunity against pneumococcus may exist in the lung when no protective substance can be demonstrated in the monkey's serum. In the experiments with intratracheal vaccine this same phenomenon was observed, namely—complete immunity against pneumococcus in the lung and the entire absence of protective substance in the serum of the vaccinated monkeys. The protection tests were carried out on mice in the usual way.

Discussion:

Dr. Huntoon: I think this work of Dr. Cecil's and Mr. Steffen's is an extremely important contribution, in that it points the way to the ultimate path of medicine, which will be to prevent instead of to cure. Many interesting points have arisen here, particularly the one as to whether this is the production of the so-called local immunity. Is it possible to produce a local immunity of some particular organ which is not enjoyed by the rest of the body? Bordet's work on dysentery brought up this old question again. In his work the mucous membrane of the gut produces an immunity against dysentery, but I remember that Dr. Zingher told us before this Society that he had failed to induce any such immunity. I shall be interested to see how the spraying experiments come out, because this would offer a method of easy application of vaccines, and it would avoid the use of the needle.

Mr. Steffen: In the spraying experiment we are spraying the monkeys with an ordinary DeVilbiss spray, and we intend to continue the spraying about three weeks. This is a very easy method of vaccination, and it does not produce any reaction. The monkeys remain perfectly lively. Even when we injected twenty, forty and sixty billion killed pneumococci into the trachea they did not show any local or general reaction.

PRELIMINARY REPORT ON THE NATURE OF THE IMMUNIZING ANTIGEN OF PNEUMOCOCCUS. TYPE I

WILLIAM A. PERLZWEIG, PH.D.

The active immunity conferred upon white mice by the subcutaneous injection of heat-killed pneumococci (type I) and of various chemical fractions of the organism was studied. It was found that:

1. By using an initial small dose of vaccine followed by a larger dose a greater degree of immunity was produced in mice than by a single large dose or by repeated large doses of vaccine.

2. The nucleoprotein obtained from pneumococcus by treatment with anhydrous sodium sulfate (Rowland's method) or by alcohol precipitation from solutions of pneumococcus in bile salts carried the active antigenic fraction.

3. On autolyzing or digesting with proteolytic enzymes the entire organism or the protein fraction, the antigen was found in the digest unimpaired, being resistant to prolonged autolytic and tryptic action.

4. On the addition of the above digests to alcohol to make a concentration of seventy to eighty-five per cent. alcohol, the antigen was recovered in the alcoholic filtrate, but not in the precipitate. The antigen is not soluble in ninety-five to ninety-nine per cent. alcohol. The alcohol-soluble antigen is soluble in neutral, acid and alkaline aqueous solutions, but is not soluble in lipin solvents.

5. The antigen is not destroyed by boiling for five minutes if in neutral or slightly acid solution, but is impaired by boiling in alkaline solution.

6. The above methods of extraction of the antigen and the dependence of heat stability upon the reaction (hydrogen ion concentration) suggest the possibility of the antigen being closely related to the antineuritic vitamine, water-soluble B.

Further work on this subject is in progress.

Discussion:

Dr. Huntoon: This work of Dr. Perlzweig is revolutionary. I have known about it for some time because I have been doing somewhat similar experiments from a somewhat different angle. I can confirm a good many things that he has spoken of, and it has long been a belief of mine that we use too much antigen for the immunizing portion of the antigen is a very small part and this can be proven mathematically. What he said about starting off with small doses is true. I have had a very wide experience with immunization of horses and I find that by giving a horse 0.1 c.c., which is a small dose in a 1,200-pound horse, then three days later 1 c.c., and then 5 c.c., you can get a horse up in three weeks as high as you can go. With streptococci you can bring a horse up in ten days to that limit. If you start a horse with 5 c.c., you throw him out of condition, and get less antibody response. After you have once sensitized him you can go on. It seems to me that the aim of the bacteriologist who is interested in active immunity and protective inoculation should be to produce a non-toxic antigen which would give neither local nor general reaction, but which would give a rapid immunity. The difference in the rapidity of immunity produced by the injection of the whole organism and the injection of the extract is very considerable. In the one case it can be done in seven days. It is almost impossible to get a protection up to the same point by giving the doses of whole antigen extending over a period of three weeks. Why should the immunity in one case be much more rapid than in the other? You have taken the burden off the animal of disintegrating the antigen by putting it into a soluble solution so that it can be taken up by the cell that produces antibody. It is all a question of ferment action.

Dr. Perlzweig: There are many intricate biological aspects of this problem that are quite difficult to solve, and which will require a good deal of time and labor. There is the question of the duration of the immunity after each of these antigens, which is a rather trying one. In some cases it seems to last quite well with the mice in question, and in some cases it does not last. Using a large number of animals, some succumb to a small dose of the infecting organism, while others, protected in the same way, withstand a very large dose of the infecting organism. I have had mice for two months after vaccination, some of which show a very good immunity at the end of that period, and others do not. There seem to be a great many factors to study that will require the exhaustive work of many men.

THE SKIN REACTION IN BRONCHIAL ASTHMA AND ALLIED CONDITIONS

NILS P. LARSEN, M.D., ROYCE PADDOCK, M.D., AND
HARRY L. ALEXANDER, M.D.

(From the Second Medical Division, Bellevue Hospital and Department of Medicine, Cornell University Medical College)

At the asthma clinic in the Out-Patient Department of Bellevue Hospital, observations were made on the "skin reaction" as a diagnostic aid in asthma and allied conditions. The mechanism of the reaction has not been established. That the skin reaction sometimes demonstrates the exciting cause of symptoms is a well-known fact. Since often no amount of questioning reveals the cause and as the removal of it gives immediate relief, there is justification for continued study of the skin reaction as a diagnostic aid.

It is also well known that a certain proportion of individuals suffering with asthma or hay fever reacts by means of an urticarial wheal, when a small amount of the substance which can originate an attack is brought in contact with a scratch or injected into the skin. The wheal exhibits irregular edges, pseudopodia developing within twenty minutes, and is usually surrounded by an area of erythema, accompanied sometimes by swelling and other signs of inflammation. The site itches and occasionally remains red and swollen for several days. Regardless of method employed, a marked reaction in a definitely sensitive skin never is difficult to elicit.

Comparison of Cutaneous and Intracutaneous Methods.—More tests can be made with less trouble and time, at the same sitting with the cutaneous or scratch method. With dry preparations (used in the scratch method), however, there is no way in which to tell when they have lost their potency. With solutions (for intracutaneous injections), contaminations which destroy the potency can be readily seen. Also, when a precipitate forms in a solution, the potency may be decreasing. One such solution which had given very good reactions for several months developed a precipitate. Cultures proved it to be sterile. Upon testing, negative reactions were obtained in several skins which then reacted well to a fresh solution of the same protein.

Clinical results showed that the technical advantages of application in the scratch method were outweighed by the increased reliability of the intracutaneous method. To illustrate with a case: A. B. developed asthma only when in contact with horses. A horse could pass, or he could ride a horse for a few minutes without symptoms, but after close contact for four or five minutes, he invariably began to wheeze. On May 1, 1921, he was tested intracutaneously on the right forearm with a solution of horse dander prepared by Dr. Coca's method. Two inches away, on the same arm, a dry commercial preparation was applied by means of a one-eighth-inch superficial scratch, upon which a drop of decinormal NaOH was applied, and then dry powder stirred into it. A control injection with horse serum was made. After twenty minutes, the intracutaneous reaction showed an irregular wheal 3 cm. by 2.5 cm., surrounded by erythema. The patient complained of itching at the site of injection. There was no reaction at the site of the scratch. The solution of horse dander, which gave this reaction, was controlled by injection into ten other asthma patients with negative results. The horse serum likewise gave no reaction. It was found that in fifteen similar instances, in thirty-one tests made, there was no definite response to the commercial preparation put on by the scratch method, although history of contact and intracutaneous methods were positive. The commercial dry preparations had been received within three months and then kept dry in the laboratory. The commercial pollen extracts gave a good reaction in most cases, whereas the dry products, especially the epidermal proteins, although effective in many instances, were so uncertain that they were unsatisfactory for routine use.

It is not possible to use the calibration devised by Walker in comparing these two methods. One can make no definite ruling as to the reading of reactions. The normal on an irritable skin cannot be compared with the normal on an unresponsive skin. It emphasizes the fact that the questionably positive reactions must be measured parallel with control injections on the same individual. These borderline reactions occur with the scratch as well as with the intracutaneous method. In such cases, an opinion can be arrived at only by repeated tests on different days, and with careful investigation of possible contact.

Comparison of the Two Methods with the Same Solutions.—To compare the scratch and the intracutaneous methods on the same individual with the same solutions, the following experiment was performed: Ten patients known to be sensitive to ragweed pollen were injected with three solutions of different strengths of this protein. These were freshly made solutions (Coca method)—Solution A, 1–100, Solution B, 1–1000, Solution C, 1–5000.

Weight of pollen in grams was the factor used in determining the strength of dilutions. The middle anterior one-third of the forearm was used, alternately placing the strongest solution superiorly and inferiorly on the different patients. Two inches away, and parallel with the injections, scratches were made about one-eighth of an inch long, and deep enough so that small red points were just visible. These scratches were kept covered with the various solutions for twenty minutes. The strongest solution was injected at the same time into two normal individuals, and had been used on many other patients routinely without reactions. Control solutions of other proteins had also been used on all these sensitive skins with negative results.

TABLE I

Comparison of Strengths of Reactions to Cutaneous and Intracutaneous Applications of Ragweed Solutions of Varying Pollen Content, in Ten Sensitive Individuals

Solution	Positive	Doubtful	Negative
Solution A			
Intracutaneous	10	0	0
Scratch	4	0	6
Solution B			
Intracutaneous	6	2	2
Scratch	1	1	8
Solution C			
Intracutaneous	5	2	3
Scratch	1	0	9
Solution A *Control patients*			
Intracutaneous	0	0	20 +
Scratch	0	0	20 +

Solution *A*—Ragweed Pollen Solution 1–100
Solution *B*—Ragweed Pollen Solution 1–1000
Solution *C*—Ragweed Pollen Solution 1–5000

It is, therefore, evident that certain individuals, whose asthma or hay fever is brought on by specific proteins, may give a skin reaction to a solution of that protein when it is injected intracutaneously and show no reaction when the same solution is applied by means of a scratch.

Relation of the Size of Scratch to Size of Reaction.—To determine whether the size of the scratch influences the size of the reaction, the following experiment was performed: As in the above experiment, the middle anterior third of the forearm was used. Eleven patients whose skins were definitely sensitive to ragweed were chosen. Two or more scratches of lengths varying from 2 mm. to 11.5 mm., and just deep enough to draw blood, were made. The scratches were covered with decinormal NaOH and dry ragweed pollen mixed with the fluid. The reactions were read in twenty minutes. The size of reaction in breadth varies with the length of the cut, but not proportionately. For instance, a scratch 11.5 mm. reacted by a wheal 11 m. in diameter, whereas, in the same patient, a scratch 2.5 mm. long gave a wheal 7.5 m. in diameter; 1 : 1 *vs.* 1 : 3.

Schloss[1] believes that the size of reaction varies, depending upon the location on the arm. To test this statement, fourteen sensitive patients were given intracutaneous injections of ragweed pollen solution at the elbow fold anteriorly and a second injection of this solution, of like amount, was given 10 cm. below. The reactions were read in twenty minutes. The reaction at the elbow was never smaller, and was usually larger than the reaction at the region nearer the wrist. There was always more erythema at the elbow site.

Other Factors which Influence the Size of the Reaction.—The strength of the solution brought in contact with the cells is another factor which determines the size of the reaction. This is shown in Table I where the same amount of fluid was injected in each instance. This fact has been made use of to determine the initial dose of prophylactic injections. When different quantities of protein solutions of equal strength are employed, a similar relation is noted. Eight sensitive patients were injected on the right forearm with 0.01 c.c., and 0.04 c.c. of a ragweed solution containing 0.3 mg. of nitrogen per c.c. The reactions were measured at the end of twenty minutes. The size of the wheal was shown to increase with increase in the amount of protein solution injected, though not always in direct proportion to it.

The skin reactions were, therefore, found to be influenced by the following factors:

(*a*) The preparation used.
(*b*) The method of application.
(*c*) The length of scratch made.
(*d*) The site of injection.
(*e*) The degree of cellular sensitivity.
(*f*) The amount of protein in contact with the cells, and the amount of solution injected.

Local Skin Desensitization.—A point still in question is local skin desensitization. Mackenzie[2] showed that by repeated injections at the same site on the same day, he could cause a disappearance of the reaction. This was repeated on two cases, as follows: The first was a male nurse sensitive to timothy pollen. He was injected nine times in the same site with timothy solution, 0.6 mg. nitrogen per c.c. The first injection was given at 9:30 A.M.; the last at 6:30 P.M. The injections were approximately one hour apart. After no injection did the skin fail to respond with a new wheal. After the eighth injection, the patient had symptoms of hay fever; also, two hours after the ninth. The eighth and ninth reactions were the largest, giving wheals with irregular edges and pseudopodia. The next morning, the forearm was still red and swollen, and another injection at the same site was followed by a markedly positive reaction.

The second case was a ragweed-sensitive patient. Four injections were given during the course of an afternoon. After no injection did the cells fail to respond, and there was apparently no decrease in reaction.

To test out the effect of weekly injections at the same site, two patients were used. After several injections, there seemed to be a definite decrease in the reactive power of these cells. The wheal became smaller, the erythema less, and when seen on the succeeding day, the site of repeated injection was clear. The control injection at a new site showed a larger reaction. One patient was sensitive to both ragweed and timothy. Both decreased as stated above, and when after three months the injections were reversed. the cells responded as at a new site. Injections were then discontinued for a period of three weeks. When the site was then reinoculated, it responded as a fresh site. On the following day, it was still red and swollen as badly as the control site. The effect of desensitization was apparently only temporary, and there was no permanent increase or decrease in the power of these cells to react.

References:

1. Schloss, O. M.: *Am. Jour. Dis. Child.*, 1921, xix, 433.
2. Mackenzie, G. M.: *Proc. Soc. Exper. Biol. and Med.*, 1921, xviii, 214.

Discussion:

Dr. Zingher: I am certain that we have all appreciated this interesting communication of Dr. Alexander. There are certain points that stand out in these intradermal tests in cases of hay fever and bronchial asthma that seem to me worth emphasizing. Anybody who has had the opportunity of seeing these tests carried out at the clinic conducted under the directions of Dr. Cooke and Dr. Coca at the New York Hospital will be impressed with certain facts.

The intradermal test seems to be highly specific. I recall just now an interesting instance of two children in one family, both of whom were suffering from asthma, and who applied for testing and treatment at different times at the clinic. In both children there was a marked reaction to an extract of rabbit's hair, and little or no reaction to the other tests. Inquiry showed that these children had slept on small pillows stuffed with rabbits' hair. Many cases of hay fever, also, give a strong reaction to a single pollen extract. This strong susceptibility is also evident in many asthmatics to individual epidermal extracts or cereal extracts.

Quite a number of these patients show a multiple sensitization to extracts from various groups; as for instance, the pollens, the epidermal extracts and the cereal groups. In some individuals one of these reactions seems to be most prominent, in others several reactions are equally prominent. I understand, however, that desensitization with an extract of the antigen that gives the most prominent reaction will also desensitize the patient against the other substances, to which he is sensitive.

The intradermal test seems highly sensitive. Many individuals give what are called negative reactions, although wheals varying in diameter from 0.5 to 0.75 cm. appear at the site of the test injections. Often it is difficult to decide whether the reaction is negative or moderately positive. Some individuals show equally prominent wheals at the site of all test injections. The diagnostic one when present appears distinctly enough as a very prominent wheal with peculiar pseudopodia prolongations. Owing to these doubtful reactions it seems quite important that fairly exact and equal amounts of the different test fluids should be injected.

Dr. Mackenzie. In the last few years there has been a great increase in the application of cutaneous reactions, and with the more widespread use, there has been a good deal of uncritical interpretation of the reaction. It is helpful and important to have such accurate observations as those which Dr. Alexander has reported to-night, and they are going to help clarify the problem. The procedure is simple, but the interpretation difficult. My experience with the cutaneous or scratch method and the intracutaneous method corroborates a good deal of what Dr. Alexander has said. There is no question about the greater delicacy of the intracutaneous test. Many patients will react to it and not to the cutaneous test. I have in mind however, one experience which I think is worth remembering when doing reactions on patients who are highly sensitive. The patient was a sufferer from hay fever and bronchial asthma in the autumn. In doing a scratch test with a 1 : 100 dilution of ragweed there was only a questionable reaction. There was a little reddening but not a definitely positive reaction. I then tried an intracutaneous test with a solution of ragweed containing 0.01 mg. of nitrogen per 100 c.c., made by extracting pure ragweed pollen with one one-hundredth normal sodium hydroxide. In a few minutes there was a large wheal four or five cm. in diameter. This went on for thirty minutes or so, and then began to subside. It was going down, and the patient had no further immediate symptoms. That night her arm swelled from the wrist to the shoulder; she had violent asthma, and broke out into urticaria over the entire body. She was confined to her bed for forty-eight hours.

As for the local exhaustion to which Dr. Alexander has referred, with Dr. Baldwin I have in press now a paper on that subject which reports observations made in the Presbyterian Hospital on a group of eight patients, repeating the test at the same site at short intervals. This was done by both intracutaneous and cutaneous methods. We found without exception that it is possible to exhaust the site locally, so that the reactivity is abolished. We found further that the exhaustion is much more rapidly effected with substances presumably more antigenic than ragweed extract. Horse serum and egg albumin have given the most striking exhaustion. However, even with our preparation of ragweed, which I presume is different from that used by Dr. Alexander, it has always been possible to exhaust the site locally, although it has taken a good many more applications than with such substances as horse serum or egg albumin. We have not tried the exhaustion method which Dr. Alexander reports, that is, repeating the tests at intervals of a week, but it is very interesting to know that at least a partial exhaustion may be accomplished in that way. I cannot feel that his failure to corroborate our observations on those two patients is of very great significance. The preparations are different, and it seems possible that exhaustion would have been accomplished if carried further. At any rate, our thirty-six consecutive attempts on eight hypersensitive patients exhausted the sites locally.

Dr. Thomas: Have you any theory to account for the variability in response to the tests for cutaneous sensitiveness, and have you noticed that patients during an attack of asthma are less sensitive to the proteins? Have you any theory also to account for the fact that there is such a discrepancy in one patient's reaction to the same test from time to time?

DR. ALEXANDER: In regard to Dr. Mackenzie's remarks, we are apparently using ragweed solution made in a different way from his, so that may account for that discrepancy. I think he has more evidence than we have, as he has eight patients and we only have two.

As to the variability in these reactions, they are very delicate and variable in so far as constant results can be obtained. There are several different factors that influence the size of the reaction, as I pointed out, and after all when size crosses the threshold from a negative to a doubtful to a positive test one must be very careful in the interpretation of the results and comparisons can be made only by repeated drawings of the reactions. During an attack of asthma it is considered probable that these skin reactions do diminish. I confess it has been our experience that they are not completely wiped out, and an attack of asthma does not seriously affect the reaction. With the exhaustion from week to week we were able to reduce reactions very materially as compared to a control site on the same arm at the same time.

We also have had a few cases where the inflammation spread up the arm after intracutaneous tests. Walker describes similar experiences with the cutaneous method. In none of these has there been any permanent damage, although occasionally a temporary attack of hay fever and asthma has been induced.

TWO CASES OF HUMAN ACTINOMYCOSIS

PAUL F. RUSSELL, M.D.

(*From the Department of Pathology, Bellevue Hospital, Dr. Douglas Symmers, Director*)

Actinomycosis in New York is not a common disease apparently, for there are records of only five clinical cases in Bellevue during the past fifteen years and among the last seven thousand autopsies in the Bellevue laboratories the two cases presented in this paper are the only ones on record. It is of course possible that one or two cases have not been diagnosed clinically but it is not at all probable that cases have been missed at the autopsy table, for sections from each case are studied microscopically.

The frequency of this disease in the United States may be judged from the fact that Erving[1] in 1902 was able to collect only one hundred cases, although the first case in this country had, according to Frazier,[2] been reported seventeen years previously, in 1885, by Murphy.

Actinomycosis is said to be more frequent in England and on the European continent. There were for example one hundred and thirty-five cases of actinomycosis in the London hospitals between the years 1902 and 1912.[3]

The first case to be presented is that of a male negro, aged forty-four, born and resident in the United States, a porter by occupation. He was admitted to a New York hospital September 2, 1920, complaining of pain in the right inguinal region of a week's duration. His family and past history were negative. Physical examination revealed some tenderness in the region of the pain and a marked psoas spasm on the right. The patient's temperature was 99° F. and the white blood cell count was 17,000 with 80 per cent. polynuclears. The condition was diagnosed as probably an appendiceal abscess that had ruptured retrocecally. An operation the following day demonstrated a deep abscess in the right lower quadrant from which several ounces of pus were evacuated. The character of this fluid is not recorded. The surgeon found it "impossible to determine the source of the pus" but the process had extended dorsally to the posterior peritoneal lining and anteriorly to the face of the ilium. A smear of the pus showed short chains of streptococci. No growth resulted from an attempted culture.

After a convalescence not apparently unusual the patient was discharged, twenty-three days after admission. The wound had gradually closed and was not draining. The final diagnosis was, "Abscess of right inguinal region."

One month after his discharge the patient was readmitted, complaining of fever, saying that he was sick. Examination of the operation wound showed slight oozing of pus and there was again a marked psoas spasm. His temperature was 99° F. but rose that night to 101.6° F., returning to about 99° F the next morning. At operation the day after readmission the granulating wound was curetted and a large cavity remained extending down to the brim of the true pelvis and up nearly to the attachment of the psoas. No cause was found for the failure to heal.

Blood chemistry was negative, the non-protein nitrogen being 32 mg. per 100 c.c., creatinine 1 mg. per 100 c.c., sugar 90 mg. per 100 c.c., and the blood Wassermann test was negative. The urine on readmission had been negative but a month afterwards it contained albumin in fair amounts. The patient was exposed to Roentgen and to sun rays. He was given massive doses of potassium iodide, but there was no improvement in his condition. For eight months he remained in this first hospital with continual drainage from the wound and a gradual failure of his general constitution. A diagnosis of tuberculosis was made, the focus being thought to be probably in the right kidney.

On June 22, 1921, the patient was discharged to Bellevue. This was ten months after his admission.

At Bellevue the man was seen to be markedly emaciated. He had a large granulating wound in the right lower quadrant with marked bulging. His lymph nodes were not palpable. The local condition was described as follows: " Large areas of protuberant granulations the size of one's hand. Tissue very soft and vascular and does not resemble chronic inflammatory tissue. It is not fibrous. It is possibly a new growth. There is much bleeding from the granulations."

A bacteriological report at this time was " prevailing organism a Gram negative, slender, non-motile, encapsulated bacillus growing readily in ordinary media but not characteristic of any known pathogenic organism."

Biopsy demonstrated " infected granulation tissue. There are some deep staining bodies suggesting actinomyces."

Repeated smears, however, did not reveal actinomyces.

A blood count showed white blood cells 7,000, red blood cells 1,600,000, hemoglobin 35 per cent. The urine contained albumin and pus.

Five weeks after admission to Bellevue the patient went into a delirious state and died. This was July 30, 1921, a year, lacking a month, following the onset of his symptoms.

The body was autopsied by Dr. Morton Ryder and myself and the following anatomical diagnosis was recorded:

Retroperitoneal actinomycosis invading the right ilium, the lumbar vertebræ (2, 3, 4, 5), the right kidney and the retroperitoneal lymph nodes. Localized pelvic peritonitis. Superficial ulceration of the bladder. Mural thrombosis of the inferior vena cava. Multiple infarcts of the lungs with gangrene. Renal calculus in left kidney. Hydronephrosis, bilateral. Hydroureter, bilateral.

" The external wound gapes widely and is filled with an exuberant growth of soft dirty brownish granulations flecked with brownish black spots. On opening the peritoneal cavity it is seen that the floor of the right iliac fossa bulges forward. The peritoneum covering it is thickened and gives a sense of fluctuation. The small intestine is moderately contracted and the coils of the ilium in the lesser pelvis are matted together by dense adhesions. An incision through the posterior peritoneum showed the fluctuant mass to consist of jelly-like yellowish material containing innumerable brownish granules the size of millet seeds. This extends inside the space of Retzius and posterior to the bladder beneath the peritoneum nearly to the midline. At this point the coils of the small intestine are matted together by dense adhesions. When they are separate an abscess cavity measuring about 5 x 5 x 1 cm., irregular in shape, is found containing greenish pus and completely walled off. The mass extends upward to the lower pole of the right kidney, which is normal in position. The tip of this pole is invaded by several nodules of soft yellowish tissue. The right sides of the second, third, fourth and fifth lumbar vertebræ are softened and black to a depth of a centimeter. The surface of the right iliac bone is bare in many places and is eroded, forming small pit-like depressions from one to several centimeters in diameter. The growth extends into Scarpa's triangle and the finger can be passed around the medial side of the femur below this.

" One or two lymph nodes in the right groin and [illegible] or two retroperitoneal nodes in front of the lumbar vertebræ are slightly enlarged, firm, and show yellowish tissue in the central portions.

"In the inferior vena cava is an adherent thrombus extending from just beyond the bifurcation upward four inches. This is about 5 mm. broad, 3 mm. thick, is yellowish and quite firm. It is smooth in some parts, granular in others and is firmly attached to the vessel wall.

"The mucosa of the bladder is diffusely reddened and over an area 2 cm. in diameter on the left side posteriorly it is roughened and black. At this site the matted coils of the intestine are adherent to the bladder.

"On section the lungs are pale red and are well aerated except in certain parts where the tissue is dark red, granular, and firm, and centrally is softened and brownish. These central areas have a foul odor and the degree of softening varies. The largest of these areas has a spongy necrotic center and the branch of the pulmonary artery leading to it is found to contain a firm yellowish thrombus lodged at the bifurcation with a prolongation running down into each branch. It is quite firmly lodged to the wall at the bifurcation.

"Microscopically the retroperitoneal tissue shows typical ray fungi in large numbers. They are immediately surrounded by polynuclear leucocytes and at a greater distance by vascular granulation tissue in which fibroblasts, plasma cells and lymphocytes are the predominating cells. A section of the lower pole of the right kidney shows typical ray fungi and in the wall of the inferior vena cava at the site of the thrombus there are typical ray fungi."

The second case is also that of a male negro. This man was twenty-five years old and had recently come from Panama. His occupation is not known. He was in coma when admitted to Bellevue and died a few hours later. The only history obtained was that he had recently come from Panama. Because his signs were obscure and his history unknown he became a case for the medical examiners of the city. A necropsy was performed by the Assistant Medical Examiner, Dr. Benjamin Schwartz, and I am indebted to him and to Chief Medical Examiner, Dr. Norris, for permission to present this case.

The necropsy demonstrated a bronchopneumonia and certain lesions in the liver, the ilium, the appendix and the colon as described below.

The liver was enlarged and was unusually adherent to the diaphragm. It was normal in color externally but the surface was bulging in one or two rounded areas. On section the parenchyma was found to be much reduced and there were present multiple abscesses varying in size from that of a pin head to one that was the size of an orange. These abscess cavities were lined by firm fibrous tissue. In some areas numerous smaller cavities had coalesced into one making the appearance that of a unique alveolar or honeycombed structure like "a sponge soaked in pus" to use Rolleston's description of a similar lesion The lining tissue had a faintly yellowish tint The pus from the abscesses was thick and viscid and yellowish-green in color. No granules were observed on casual examination. A methylene-blue stained smear revealed no typical picture although there were seen numerous homogeneous rounded bodies with suggestive feathery edges.

The wall of the colon was thickened and in places quite nodular. The mucosa presented numerous irregularly placed superficial round and oval ulcers not over 1 cm. in diameter. These apparently involved only the mucosa and to a slight extent the submucosa. The edges were not raised or undermined and the ulcers were not typical of tuberculosis, typhoid fever or amœbic dysentery.

Externally the appendix, ilium and cecum were normal and their mucous surfaces showed nothing unusual.

Because a stained smear of the pus had been negative and because of the general characteristics of the lesions, together with the fact that the patient had recently come from Panama, a tentative diagnosis was made of amœbic abscesses and ulcers with actinomycosis to be ruled out microscopically.

Routine sections revealed typical ray fungi and no evidence of amœbic abscesses. The appendix was then sectioned serially and in the submucosa and muscularis was found an abscess extending longitudinally for a distance of about half the organ. No defect in the mucosa was demonstrated and the serosa was intact. The abscess appeared yellowish and granular with thin fibrous trabeculæ throughout. A similar abscess was discovered in the wall of the terminal ilium but gross serial sections of the colon did not reveal abscesses. Microscopical sections revealed typical ray fungi in the wall of the appendix and in the ilium. No ray fungi were found in sections of the wall of the colon. The possibility of the lesions in the colon being due to the actinomyces is greater because of the similarity between these lesions and those in a case described by Chiari [2, 32] who says that primary actinomycosis of the intestinal tract manifests itself as a superficial invasion of the mucous membrane in the formation of whitish patches or in the more diffuse variety by the formation of nodules beneath the mucosa. These nodules undergo degeneration, ulcerate and rapidly extend. However since no ray fungi were demonstrated in the wall of the colon a diagnosis of actinomycosis of the colon can not be made.

Pus had been saved from this case and a more careful examination revealed characteristic granules. A majority of these were like sand grains in size and color. Some, however, were dark brown and some were sulphur yellow. All were soft. When some of this pus was shaken in a test tube of normal saline the grains were easily isolated from the viscid suspension and could be demonstrated clinging to the sides of the tube. Granules pressed between a cover slip and slide presented microscopically typical unstained mycelia. An anaerobic culture in dextrose agar had been made at the time of necropsy and a growth of *actinomyces bovis* was isolated.

In this case the primary lesion may very likely have been in the appendix if we accept the views of many observers. If so the fungi traveled via the blood stream to the liver.

The case illustrates the possibility of missing a correct diagnosis without particular care and special methods of examination Pus in suspected cases should always be examined carefully for granules for it is very easy to fail to see them. The simplest method is to shake a small amount of the pus in a test tube of water or normal saline. Having isolated a granule, it may be pressed between two glass surfaces and examined microscopically. Typical mycelia may readily be identified. Clubs will rarely be present in the human cases. A methylene-blue and a Gram stain will further aid in the diagnosis, but are confusing if applied to a smear of pus rather than to an individual granule that has been washed in saline. It should be remembered that the granules are by no means always the typical sulphur granules of the text-books. On investigation of the literature the following color designations were found applied to the granules: white,[5] pearly white,[1] grayish white,[6] yellowish white,[1] black,[8] brownish black,[7] brown,[9] gray,[10] pearly gray,[1] yellow gray,[11] cream colored,[12] red,[13] yellow [14] sulphur yellow,[16] lemon yellow,[11] whitish yellow,[15] green.[7]

The granules have been described as granules, grains, specks,[8] like sand,[17] like minute pearls, like minute raspberries,[9] like fish roe,[14] like gun-powder,[8] like rice particles,[16] and they may be soft, firm or calcific.

The color of the pus has been described as white, cream, yellow, chocolate, and green.

Routine sections of tissue were stained with hematoxylin and eosin. Mr. Wm. Johnson, technicist in the Bellevue laboratories, prepared other sections stained with carbol fuchsin, then decolorized and counterstained with picric acid. In these the ray fungus stands out as a red aster on a yellow background.

In none of the sections from the two cases presented were ray fungi seen with typical clubs. A typical actinomyces rosette is made up first of a central felt-like core of long, thin, branching filaments irregularly disposed but with a general radial arrangement and not decolorized in the Gram method of staining. Secondly, there may be at the periphery of the central core a crown of pear-shaped swellings of the terminal ends of the filaments. These are Gram negative. Hiss and Zinsser[44] believe that they represent a form of degeneration and that they are the hyaline thickened sheaths of the threads. They are more frequently absent than present in the rosettes from man but are nearly always present in those from cattle. Thirdly, there have been described coccus-like bodies that resemble spores and that led to the classification of the actinomyces as a spore-bearer. They are not spores, however, according to modern workers, but are either symbiotic cocci or else degeneration products.

Although the fungi in these cases did not show the clubs, they were typical in all other respects.

Conclusions:

In conclusion it may be noted that the chief problems in the study of actinomycosis are first as regards the method of infection and secondly as regards the method of treatment. Neither of these phases of the disease has been satisfactorily dealt with. Where the fungus is when not actively invading the tissues, how it gets into these tissues, whether it is a normal inhabitant of the various tracts of the body, whether it hides away in tonsils and dead teeth, all of these questions are as yet unanswered although there are many more or less attractive theories to explain them.

Finally, it should be emphasized that in every chronic suppurative lesion resembling tuberculosis, syphilis or a neoplasm, actinomycosis should if possible be carefully ruled out. This is especially true of atypical pulmonary disease where repeated sputum examinations should be made with a view to finding the ray fungus in the absence of the tubercle bacillus.

The diagnosis of actinomycosis is never established until typical ray fungi have been demonstrated. These may be found in tissue, in pus, in sputum, in urine, in feces, in spinal fluid, and most rarely in blood.

Discussion:

DR. HAAS: I happen to have at the present time a case of intestinal actinomycosis in a young man of twenty-one. He is dying now. The onset was almost identical to that of the case Dr. Russell described. He was first seen about two and a half years ago, when he gave a history of some abdominal distress during the previous week, and on the day of onset sharp pain in right iliac with nausea. When examined there was moderate shock, with a temperature of 100.5°. There was slight rigidity and tenderness of the right iliac region, and I decided it was probably appendicitis. Dr. Elsberg was called and that evening the boy was operated on. There was no inflammation of the appendix, but the ilum near the appendix showed a perforating ulcer which was covered by omentum. There was some free sero-pus in the abdomen. At that time neither of us had any suspicion of what it was. Everything went along very well for a number of days, when after a rise of temperature a fecal fistula formed. This resisted all methods of treatment, and soon the subcutaneous tissue around the wound disappeared, and the skin with it, and there was an area about as big as the palm of the hand which was entirely exposed. At this time search was begun for the fungus, the differential diagnosis lying between syphilis, tuberculosis and actinomycosis. Nothing was found corroborative of any of these diagnoses. This condition continued for a long time, and it was then decided to remove the sinus. A second operation was performed and the sinus excised widely, and it seemed as though the result would be good. The wound healed very well, and just as the boy was to be discharged, the wound perforated, and the previous experience was repeated. As a matter of fact the fungus was not found until pus from a freshly perforating sinus was obtained. The boy now has five sinuses in his abdominal wall. It is only at the moment of perforation that one is able to find the fungus. Even after the character of the infection was known, examination of the pus failed to show the fungus again. The patient is now having very violent back-aches so that the vertebræ are perhaps becoming involved. So far as therapy is concerned, neosalvarsan, large doses of potassium iodide, methylene blue and emetine have been given, and as a last resort radium was tried, and that just about finished him. It was very interesting indeed to see how that treatment accelerated and intensified the progress of the disease. We have seen the same thing occur when the x-ray was used therapeutically in pulmonary carcinoma, the treatment producing intense toxemia and death within a short time.

Dr. Moschcowitz: Actinomycosis is not as rare if you look for it. I have seen a considerable number of cases—a few of them in the lung, a very few in the abdomen, and a good many in the skin and bones. There is one point in connection with the diagnosis of actinomycosis which is emphasized by Dr. Libman, and that is that tenderness is a prominent symptom. We all know that the prognosis is bad. We hardly realize how bad it is. I have seen a number of patients in whom the lesion is apparently healed, and in whom months or years later either the wound breaks down, or a focus appears in another part of the body.

Dr. Russell: In regard to the frequency of actinomycosis observers differ. Dr. Moschcowitz, for example, states that he has seen a considerable number of cases and believes that the disease is not rare. On the other hand some observers have encountered it but rarely. Griffith[45] for example reports two cases as the only ones he has seen in fifteen years of active practice. He believes that the disease is rare and states that his colleagues have the same opinion.

In Bellevue as recorded above there have been only five cases in fifteen years. In the records of Roosevelt Hospital there is listed only one case. At New York Hospital there are only three cases in the records. At Bellevue two cases have been autopsied in fifteen years; none have been autopsied at either Roosevelt or New York Hospital.

Undoubtedly cases are missed clinically but since all diseased tissues are sectioned at the post mortem table and a careful microscopical study made, it does not seem probable that many cases are missed that come to necropsy.

As to the frequency with which different parts of the body are involved there have been a number of reports. Ruhrah[16] in his first report had collected 632 cases throughout the world and reported actinomycosis primary or maximum in

	Per Cent.
Head and Neck	57
Gastro-intestinal Tract	21
Thorax	15
Skin	2
Doubtful	5

Later he[16] had collected 1,094 cases with practically no change in the above percentages.

Taking the reports of six series of cases the following averages are obtained:

	Per Cent.
Face and Neck	55
Abdomen	23
Thorax	17
Skin	5

In regard to the frequency with which the various organs are involved in the first place it may be noted that practically every organ in the body has been attacked by the ray fungus. But in abdominal cases the appendix and the cecum seem to be the site of election. Hinglais[17] found the appendix involved in 60 per cent. of his cases. Kelley[18] and Cope[19] state that the appendix is the commonest site of infection, while Waring,[20] who reports seven cases, believes that the cecum is the commonest site.

Actinomycosis of the liver, according to Rolleston,[4] is rare. He states that Auvray in 1903 could collect only thirty-one cases.

Secondary actinomycosis of the kidney has been repeatedly observed. Garceau[21] for example reports 128 autopsies collected from various sources in which there was actinomycosis somewhere in the body and in eleven of these cases the kidney was involved. According to Ransohoff[22] the only case of primary actinomycosis of the kidney was reported by Israel. In this case the organisms were identified in the urine and in pus from a lumbar fistula.

Robinson[23] in 1919 collected nineteen cases of actinomycosis of the female genitalia, reporting a case in which he found it in both ovaries in a patient fifteen years old.

Hodenpyle[24] collected thirty-four cases of pulmonary actinomycosis, and Hichens[33] gives a good account of this form of the disease.

The heart may be affected by metastases or by continuity.[25]

Actinomycosis of the brain has been reported, but it is rare.[27]

Cases have been reported involving the stomach,[34] gall bladder,[35] breast,[36] tongue[37] larynx,[38] skin,[18, 39] retina,[40] conjunctiva,[41] salivary gland[42] and elsewhere.

As both Dr Haas and Dr Moschcowitz have observed, the course of actinomycosis is chronic. It is not infrequently recorded that after an apparently successful appendectomy, the patient, having been discharged as cured, will in the course of a few months to a year return with a draining wound or an abscess and at this time a second operation and more careful examination will disclose the organism of actinomycosis in the pus.

The mortality is fearful In Keen's surgery the mortality from all cases is given as 47 per cent. Frazier[2] says the mortality in cases of abdominal actinomycosis in the United States has been 71 per cent.

Jiron[2] gives the following mortality statistics:

	Per Cent.
Cerebral	100
Thoracic	83
Abdominal	71
Face and Neck	11

So far no satisfactory treatment has been devised as the above mortality statistics demonstrate. Consequently every observer who has had two or more cases has experimented along lines of his own devising.

Potassium iodide is mentioned in all text-books but it has never been shown that there is the slightest scientific basis for the use of this drug which was introduced empirically by Thomassen[29] in 1885 for actinomycosis of the tongue in cattle and which was later proclaimed by Nocard[12] to be specific.

Harbitz and Grondahl[7] have demonstrated that the *actinomyces bovis* will grow luxuriantly on potassium iodide media in which the iodide is present in from 0.25 to 2 per cent. concentrations. Logically they doubt the value of this drug in the disease.

In fact potassium iodide may even be harmful. Jobling and Peterson[30] believe as a result of their experiments that the iodide neutralizes the action of the agents which prevent the solution and absorption of necrotic tissue and at the same time therefore lays bare to the action of the real germicidal agent the infecting organism that has been protected by the necrotic tissue. If this is true potassium iodide may accelerate this disease, for there is no known germicidal agent that can be administered to destroy the actinomyces in the tissues. Hence the organism may be speeded in its journey to other parts of the body.

Bevan[43] tried copper sulphate on the theory that it is effectual against vegetable parasites and he has had some success with it. Later he recommended using both potassium iodide and copper sulphate.

Many other drugs have been tried with occasional cures.

Autogenous and stock vaccines have been used.

X-ray and radium have been of some value apparently in a few cases. Heyerdahl[31] reports six cases of cervico-facial actinomycosis cured by radium.

But in most of the series reported where various methods have been used the mortality has been in accordance with the average figures as given above, no matter what the treatment. For example Colebrook[12] advocates surgery plus vaccines. In his series, nine out of eleven cervico-facial cases were cured, all six of his thoracic cases died, and five out of the six abdominal cases died.

There is no doubt that effectual drainage should be established, but as to the medical and mechanical treatment beyond this there is confusion.

Bibliography

1. Erving: *Bull. Johns Hopkins Hosp.*, 1902, xiii, 261.
2. Frazier: *Keen's Surgery,* Vol. 1, p. 524.
3. Norris and Landis: *Diseases of the Chest,* 1917, p. 381.
4. Rolleston: *Diseases of the Liver*, 1916, p. 381.
5. Wright: Osler and McCrae's *System of Medicine*, 1913, p. 1033.
6. Wright: *Reference Handbook of Medical Sciences,* 1913, Vol. 1, p. 104.
7. Harbitz and Gröndahl: *Am. Jour. Med. Sc.,* 1911, cxlii, 386.
8. French: *Differential Diagnosis*, 1920, p. 677.
9. Achard: *Albutt's System of Medicine,* 1912, Vol. 2, part 1, p. 324.
10. Lord: *Oxford Loose-Leaf Medicine,* 1920, Vol. 5, p. 397.
11. MacLeod: *Diseases of the Skin*, 1920, p. 431.
12. Colebrook: *Lancet, London*, 1921, 1, 893.
13. Stengel and Fox: *A Text-Book of Pathology,* 1921, p. 518.
14. Sutton: *Tice's Practice of Medicine*, 1920, Vol. 4, p. 119.
15. Barker: *Monographic Medicine*, p. 326.
16. Oertel: *General Pathology*, 1921, p. 72.
17. Murphy: *Keen's Surgery,* Vol. 6, p. 573; Vol. 4, p. 760.
18. Kelly: *Appendicitis,* 1909.
19. Cope: *Brit. Jour. Surg.*, 1915–16, iii, 55.
20. Waring: *St. Bartholomew's Hospital Report,* 1905, p. 197.
21. Garceau: *Tumors of the Kidney*, 1909, p. 307.
22. Ransohoff: *Keen's Surgery*, Vol. 4, p. 233.
23. Robinson: *Surg., Gynec., and Obst.,* 1919, xxix, 569.
24. Hodenpyl: *New York Med. Jour.*, 1890, Dec. 13.
25. Letulle and Hufnagel: *Bull. de l'Acad. de Med., Par.,* 1919, lxxxii, 120
26. Howard: *Jour. Med. Research*, 1903, ix, 301.
27. Vollinger: *München. med. Wchnschr.,* 1887, No. 41, p. 789.
28. Enriquez and Sicard: *Lancet, London*, 1904, June 4, p. 1585.
29. Thomassen: *L'Echo Vet*, 1885.
30. Jobling and Peterson: *Arch. Int. Med.*, 1915, xv, 286.
31. Heyerdahl: *Jour. Am. Med. Assn.*, 1919, lxxiii, 1928.
32. Chiari: *Prag. med. Wchnschr.*, 1884.
33. Hitchins: *Brit. Med. Jour.*, 1905, Nov. 4.
34. Robson: *Keen's Surgery*, Vol. iv, 478.
35. Robson: *Diseases of Gall Bladder.* Ed. 3d, p. 173.
36. Furiez: *Keen's Surgery,* Vol. iii, p. 574.

37. Binnie: *Ibid.*, Vol. ii, p. 442.
38. Brewer: *Ibid.*, Vol. iii, p. 543.
39. Pels: *Jour. Cutan. Dis.*, 1919, xxxvii, 740.
40. Mueller: *Klin. Monatsbl. f. Augenh.*, March, 1903.
41. Brunetiere: *Jour. de Med. de Bordeaux*, 1920, xci, 459.
42. Soderlund: *Acta chir. Scandinav.*, 1921, liii, 189.
43. Bevan: *Jour. Am. Med. Assn.*, 1905, xlv, 1492.
44. Hiss and Zinsser: *Text-Book of Bacteriology*, 1918, p. 623.
45. Griffith: *Surg., Gynec., and Obst.*, 1921, xxxiii, 5.

ENDOCRINE GLAND STUDIES, INCLUDING GOITRE IN INDIA *

ROBERT McCARRISON, M.D., F.R.C.P., LT.-COL.

Indian Medical Service

I desire in the first place to thank you for the honor you have done me, and the Service to which I belong, in inviting me to speak to you this evening. I see in this audience so many whose researches have made their names familiar to students of endocrine disorder that it is with a certain diffidence I bring before you the results of my own investigations, carried out for the most part in the far distant Himalayas.

It is now some twenty years since Fate sent me to a part of the world where goitre was extremely common. I found myself, in 1902, posted as agency surgeon in hill stations situated in the Hindu-Khush region of Northern India, first in Chitral and later in Gilgit. The nearest railroad station is at Rawalpindi, some twenty days' journey by tonga, boat, horse and mule from Gilgit. One has, therefore, some excuse for speaking of one's work as having been done under isolated conditions. The facilities for intercourse with one's fellow-workers were, of course, very limited indeed; while access to medical literature was very restricted.

In Chitral and Gilgit goitre was so common that in some villages no one was free from it. In localities where its endemicity was high, men, women, and children alike suffered from it. In the village of Awi in Chitral, for instance, about sixty per cent. of the children were born with congenital goitre, while many were cretinous, and every man, woman and child was goitrous. The villagers used to say of this village that "even the trees had goitre"; there was some excuse for their thinking so, since many of the trees did have curious nodular growths on their barks. These excrescences arose, of course, from causes other than those which gave rise to goitre. The goitrous state of this village, which was not exceptional, gives an idea of the extent of the prevalence of the disease and of its congenital manifestations. But while it was so prevalent as this in one village, another situated, it might be, within pistol-shot of the first might have no goitre at all. This circumscribed distribution of endemic goitre has always been a very great puzzle.

---

* Stenographer's report of a lantern slide demonstration given before the New York Pathological Society on November 9, 1921.

When I first went to Chitral in 1902 most of the current views as to the causation of goitre centered around the water-supply: it was thought to be due to excess of lime or of magnesium in the water, or to be due to snow water. So knowing nothing, premising nothing, I began to occupy myself in the study of its etiology. The first observation of any importance which I made was as follows: There were on the Gilgit-Fan eight villages situated one above another on a single water supply. I made a survey of the endemicity of goitre in each of these villages. Every man, woman, and child was examined. It was found that in the first village there was eleven per cent. with goitre. The water was not confined to the banks of the stream, but was used to irrigate the cultivated land between the villages. The irrigation water joined the main stream at the second village, and in this village the percentage of goitre had risen to eighteen. The stream spread over the fields, irrigating them, and came to the third village where the incidence of goitre was twenty per cent. Below this point the main stream was joined by another of exceptional purity, and the fourth village showed a drop in the incidence of goitre to eighteen per cent. I need not continue with this detailed description, but I will tell you that the incidence of goitre gradually increased until ultimately it reached forty-five per cent. in the eighth and lowest village on the common water-supply. This observation was made in 1906. Later Dr. David Marine, than whom there is no one who has contributed more to our knowledge of thyroid disease, made a similar observation with regard to artificially bred trout. He found that goitre gradually increased from above downwards in the tanks holding the trout, and that a diminution in the incidence of goitre occurred when the stream was joined by another water-supply. Since then I have pursued one line of investigation and Dr. Marine another, but to-day finds us in substantial agreement. I took the line that the increasing incidence of goitre in villages situated one above another on the same water-supply was associated with the increasing bacteriological impurity of the water. I thought that if this were the case, and if bacteria were concerned in the production of goitre, then the disease might be curable by intestinal antiseptics. Consequently, a man who had a well-marked goitre without adenomatous degeneration was given large doses of salol. After he had been taking salol for ten days or so and no appreciable improvement had been noted, I went on tour, leaving him still on salol. At the end of six weeks, I returned and found his goitre had disappeared. I then tried thymol in other cases, using the drug in large doses, and I got results with this drug which I will presently show you on the screen; they justified my assumption that bacteria in the digestive tract were concerned in the genesis of goitre.

Before I go on I wish to say a word or two about the goitres which one found in Chitral and Gilgit. In the first place, Graves' disease, or exophthalmic goitre, was practically unknown. I can count on the fingers of one hand the cases of Graves' disease which I saw among the indigenous inhabitants of Gilgit; and when one is dealing in thousands of cases of goitre that is a very striking thing. The cases of Graves' disease which I did see were definitely associated with fright or shock. Another point which I wish to make is this, that throughout India Graves' disease occurs but rarely amongst the indigenous inhabitants. Some three or four years ago I sent a request to the great Presidency hospitals in India—at Calcutta, Bombay, and Madras—where the number of patients coming to the hospital in a year is very large, asking the superintendents to let me know the numbers of cases of Graves' disease admitted amongst various races of India during a period of ten years. They sent me figures which showed that it was very rarely found among the indigenous inhabitants, although it did occur amongst those who were strangers to the land—Europeans, Parsees—and was also comparatively common among Anglo-Indians. During the war, however, I came across a number of cases of Graves' disease among Indian troops who had been to Europe. It is a point of considerable interest that among men who had come from India, where Graves' disease is practically unknown, examples of this malady should have been encountered. It would seem that the conditions of service in Europe were such as to favor its development in Indians, who in their own country are rarely affected by it. I throw out the suggestion, therefore, that Graves' disease is a disease of civilization. Another point is this: almost all cases of goitre of long standing in Gilgit ultimately become adenomatous, and yet I never saw hyperthyroidism associated with thyroid adenoma. One reads a very great deal about " toxic adenoma." I have never seen it in the Himalayas.

With your permission I will now show you some slides. This one represents a goitrous patient who was the first man I ever treated with thymol. He looked after a herd of cattle and continued this occupation throughout the whole course of treatment. He came regularly to hospital for three and a half months. He had a goitre which caused the circumference of his neck to measure 42 cm. The next picture shows the same man after three and a half months' treatment by thymol, when his neck measured 36.5 cm. There is no doubt about the result. The man did his customary work; he was not a resident patient in the hospital, and to my knowledge he did not get any other treatment. I collected many more such cases. Messereli of Lusanne has published many cases confirmatory of this action of intestinal antiseptics in recent cases of endemic goitre.

Now came the next step. I assumed, if I were dealing with intestinal organisms having to do with the causation of goitre, that I might get results by preparing vaccines from them, and treating recent goitres with such vaccines. Here is a picture of a man with goitre that had caused the circumference of his neck to measure 42 cm. before vaccine treatment was commenced. I gave him an autogenous *B. coli* vaccine in large doses once a week. Within a few weeks the goitre had disappeared. In those days my methods of standardizing vaccines were not so accurate as they would be to-day. I was probably giving this man much larger doses than I thought. He, as well as others similarly treated, had marked reactions after the injections. Here is another man who was treated by vaccines. This case is interesting, because the vaccine with which he was treated was made from a spore-bearing organism obtained from the fecal discharges of one of my polo ponies that had developed goitre. I injected it into this man in large doses. He was so greatly improved after several weeks' treatment as to show little trace of his goitre. These results were obtained with vaccines made from various intestinal bacteria. There was no specificity about their action.

I have shown you three or four of these cases, and I think you will have observed from the pictures that apart from the improvement in the goitre itself, the general appearance of the patients greatly improved. Any hypothyroidism which they may have had cleared up. The skin became much finer and softer, and the face thinner and less puffy looking,—a result noted also to follow cure by iodine, by thyroid extract, by soured milk, or by intestinal antiseptics. Precisely how large doses of vaccines may bring about this result, or what component of the bacteria is responsible for it, I do not know.

The next step in my work was to see whether I could induce goitre in man and animals. I have made a great number of attempts to do so. This picture shows the trachea with the attached thyroids of a number of rats. The top row shows those of the control white rats. The second row shows the thyroids of wild rats from the locality in which the experiment was conducted. So you will see that the white rats did not have any goitre when the experiment was started. I got a large cage and divided it into three compartments of equal size; in each I put six white rats. In one compartment were the controls. In the second were rats which were fed on the residue left on the candle of a Berkefeld filter after filtration of a fecal emulsion from a goitrous person. In the third were rats which received the fecal filtrate. One hundred per cent. of the animals which received the fecal material developed goitre while the controls on the same food and in the same cage did not. The result of this experiment strengthened me in my assumption, which was becoming a belief, that goitre in Gilgit was intimately associated in its origin with bacterial organisms resident in the alimentary tract, and reaching the tract by way of water or contaminated food. At that time I only thought of such organisms as contributors of positive agents to the thyroid's harm. I could not think of them apart from the direct action of their toxins, so I believed for a time that goitre was caused by the direct action of microorganisms or of their toxins on the thyroid gland, and I continued my search for a specific bacterial excitant of the malady. I have altered that view to some extent; and have abandoned the view of a specific bacterial excitant, while still maintaining my position as to the important relation that exists between bacterial agents and the genesis of goitre and of thyroid disease in general.

Before starting these experimental investigations on a large scale, I had to establish a base line of normality for the thyroid gland of the animals (rats) with which I was working, because most animals kept in confinement showed some degree of thyroid change. What I did was to ask the plague medical officers to send me a large number of the rats which they caught in connection with anti-plague measures. They sent me some six hundred wild rats from various parts of India. I found some interesting things in connection with these rats. In those from the sea-coast and from about the level of the sea-coast, the thyroid had in the majority of cases the appearance shown on the screen: the acini were well defined and distended with colloid, low cuboidal or flattened epithelium lined each acinus, and the organ was in its colloid or resting phase. On the other hand, a number of them were like this. The vesicles were smaller, the colloid was much thinner and less plentiful, the acinar cells were higher, and the gland was in a condition of physiologically active secretion. About twenty-five per cent. coming from the sea-level were of the latter type. When I examined the thyroids of rats from localities at a height of six thousand feet or more above sea-level, the greater proportion of them were found to be of the second type, that is to say, of a type which one associates with greater physiological activity. It seemed, indeed, that the farther from the sea-coast or the higher the altitude, the more physiologically active was the thyroid, an observation that may not be without significance in connection with the preference of goitre for mountain ranges.

The next specimen is a section of an experimentally produced goitre in a rat; you will see that there is evidence of marked hyperplasia; the amount of colloid is very small; the acinar cells are high; there is a tendency to acinar budding, and the thyroid is beginning to assume the histological characters which it is customary to connect with Graves' disease.

The next step in my inquiry was to see if I could produce cretinism and other congenital manifestations of thyroid defect; so I fed rats throughout pregnancy on fecal material or on bacterial cultures from the feces of goitrous persons. Here is a litter of three young rats aged twenty days. The mother of these animals was fed on milk and unleavened bread, and received the fecal filtrate from an emulsion of feces. The middle one is very much smaller than the rest. It has curvature of the spine and is but sparingly clothed with hair. After I had photographed this litter, the badly grown animal in the center was eaten by its parents. In order to avoid that risk in future I killed the young that were born to mothers fed on fecal material, four days after birth. This specimen shows a four-day-old litter, one of which is a cretin.

This is its thyroid and parathyroid glands. The gland was devoid of thyroid structure and was made up largely of connective tissue cells; the thyroid apparatus was congenitally atrophic and there was no evidence of vesicle formation nor of colloid. It was thus shown that there was something in the fecal material from goitrous persons which when administered throughout pregnancy to goitrous rats was capable of causing cretinism in the young.

The next specimen shows the effect of fecal anaerobes when fed to pregnant rats in causing hemorrhagic lesions on the parathyroid glands. I found such lesions as these in quite a high proportion of newborn rats whose mothers had received, throughout pregnancy, anaerobic cultures of fecal bacteria in glucose broth.

After dealing with rats I went on to larger animals. I procured from Delhi a number of female goats of the first year that had never had offspring. They were brought up to my laboratory, which was situated at a height of 6,900 feet above sea-level. Eight were kept as controls, and twelve were used for the actual experiment. Both controls and experimental animals received the same food; there was no difference in their intake of iodine. The only difference was that I muzzled a number of my controls so that they could not eat anything except what I gave them. I fed these goats for several months on cultures of fecal bacteria. On one day they received 10 c.c. of a 24–hour culture in 2 per cent. glucose broth, on the next a 48-hour culture, on the third a 72–hour culture, on the fourth a 24–hour culture, and so on. After several months the thyroids of most of them were palpable. They were then impregnated, and during pregnancy these cultures were continued. They gave birth to young that were all dead-born, hairless, and having enormous goitres. The controls on the other hand which received no cultures gave birth to kids that were fully developed and had excellent coats. Several among the control kids had small congenital goitres which disappeared shortly after birth and one was born dead but fully developed. The contrast was so great that it is impossible to escape the conclusion that the cultures referred to contained bacteria or their products that greatly favored the development of congenital goitre and cretinism.

At one stage of the proceedings I took water from the last village on the Gilgit water-supply and passed it through the candle of a Berkefeld filter. Sixteen young men, including myself, drank, night and morning, under strictly controlled conditions, a cupful of the residue left on the candle of the filter. I had no medical colleague who could check my investigations, so I was forced to rely on a member of another profession—an engineer. I thought he would probably be capable of noticing any changes in the size of our necks. He measured my neck before the experiment commenced and after it was completed. At the end of the experiment he gave me a certificate which I came across among a lot of old records a short time ago. It said that I had a swelling on the right side of my neck, and a bridge of tissue across the windpipe that rose and fell on swallowing, and that neither of these were there two months before. So I think you can take it that I did have a goitre, as did also several of the others. The controls remained goitre-free.

Having thus produced goitre in man and in animals; having also produced the effects of thyroid deficiency in the offspring; and having cured goitre by intestinal antiseptics and by vaccines, the next step was to prevent it on a large scale. The opportunity presented itself when, in 1913, I was asked to report on a school just below Simla where goitre was extremely prevalent. This school is intended for the boys and girls of British soldiers who cannot be sent home to England for their education. They get an excellent education there, but unfortunately they suffered greatly from goitre. You will see from the chart which I now show you that among boys between five and ten years of age something like eight per cent. were goitrous. Among boys of sixteen and over, forty-three per cent. were goitrous. Among the girls the incidence of goitre was even more marked. In those between ten and fifteen years of age fifty-nine per cent. were goitrous, while sixty-four per cent. of the girls over sixteen were goitrous. This state of affairs was very serious, especially when one knew, as I did then, that approximately five per cent. of all goitrous mothers give birth to cretinoid children. The boys and girls were in separate parts of the school; it was convenient to use the boys for the purpose which I had in view. I thought, after a study of the site and the water-supply, that the disease might be due to fecal pollution of the water; bacteriological examination every day over a long period showed it to be badly contaminated. Consequently I began to purify the water, using Nesfield's reagent which contains iodine. I used this reagent for about seventy-five days. After that I used chlorine. The water given to the boys was treated in this way. That given to the girls was not so treated. After six and a half months there was a drop from forty-three to twenty-four per cent. in the cases among boys, whereas among the girls, where the water was not treated in this way, there was a rise in the incidence of goitre. We reported on this observation, emphasized the beneficial effect of these reagents in the purification of the water as a means of preventing the disease, and recommended the continued use of chlorine as a purifying agent, or the introduction of another water-supply. It was ultimately decided to follow the latter suggestion. It may be that I laid too little stress on the specific effect of the iodine on the thyroid gland as an essential factor in reducing the incidence of goitre in this school. I have no doubt that a part of the good effect was due to the specific action of iodine, but equally no doubt that the removal of the bacterial impurity of the water was also concerned in bringing it about, for when a new water-supply was introduced the disease gradually disappeared. I have lately been officially informed that at the present time goitre is no longer prevalent in this school. The evidence that fecal pollution of the water had to do with the presence of goitre in this school is very strong. Dr. Marine's work, with which you are all familiar, shows the ease with which this very insidious disease can be eradicated by the prophylactic use of iodine. But this does not mean that the bacterial factor in its causation can be ignored, for it would seem that in the presence of certain bacteria in the alimentary tract more iodine is needed to insure healthy thyroid action. The prophylactic use of iodine is a measure of the utmost importance. Anyone who has seen the moral and physical degeneration which can result from goitre must realize what a tremendously important thing it is that goitre should be prevented. We cannot as physicians emphasize too strongly the very great importance of preventing this disease in localities where prevention can be undertaken. It is a measure of the highest national importance in all countries where endemic goitre prevails.

We have then two important facts relative to the genesis of endemic goitre: first, that bacteria in the alimentary tract can be concerned in its genesis, and second, that small amounts of iodine will prevent it—extraordinarily small amounts. There must be some connection between these two facts. The ultimate cause of goitre is of course the undue stimulation of the thyroid gland consequent on the insufficient supply of iodine. I now think that this supply may be interfered with in a number of different ways: by insufficient intake of iodine, which is comparatively rare; by imperfect absorption of iodine; by insufficient assimilation of iodine; or by its imperfect utilization by the thyroid gland. It is within the orbit of these possibilities that we must seek for the true explanation of the influence of bacterial agents. It is to be remembered that goitre can and does arise in many cases where the provision of iodine is inadequate. Bacterial agents may act by preventing, in some way, the absorption, or by interfering with the assimilation of iodine, or by impairing the utilization of iodine by the thyroid gland.

The next part of my address will provide additional matter for consideration in this regard, and bring into prominence nutritional factors in thyroid disturbance. I wish now to show you some of my more recent work on the effects of faulty foods on the thyroid gland. This picture shows the normal thyroid gland of a monkey; contrast it with the next which shows the thyroid gland of another monkey that was fed for a considerable time on a diet of autoclaved rice and butter, that is to say, on a diet which is deficient in vitamins B and C, and disproportionately rich in starch and in fat. The vesicles are small, the colloid is thin, and there is a great deal of congestion. The dark areas around the alveoli are distended blood spaces. That is an effect which I have noticed in a high proportion of animals fed in this particular way.

The next picture shows the normal parathyroid gland of a monkey. I wish you to contrast it with this which shows the intense congestion of this organ that is brought about as the result of a food deficient in vitamins and ill-balanced in other respects. You will remember that hemorrhagic lesions of the parathyroids can be produced in newborn rats by feeding their mothers during pregnancy on anaerobic cultures of fecal bacteria. Here is a similar result, but brought about by faulty food. It would seem almost as if the deficient food had enabled anaerobic microorganisms to exert their harmful effect on the parathyroid glands.

This chart indicates that the endocrine organs, with the exception of the adrenal glands and the pituitary body, undergo atrophy in consequence of a diet deficient in vitamins. The adrenal glands enlarge, and the enlargement occurs both in inanition and in that form of starvation which is known as avitaminosis. This dark column represents the average weight in milligrams of the adrenal glands per kilogram of body weight in control pigeons. This weight is approximately 93 mg. In pigeons that were fed on polished rice the weight of the adrenals reached as high as 160 mg.

The thyroid gland undergoes a considerable amount of atrophy in consequence of food deficiencies, so that their effect on one pair of organs—the thyroid and the adrenal—that are so intimately concerned with metabolic regulation, is to cause a diminution in the size of the former and an enlargement of the latter.

I will show another chart in order to emphasize a further point. This chart represents the effects on the thyroid and adrenal glands of pigeons of excessive feeding with mixed millet seeds, peas, and butter. In contrast to the effect of deficient feeding, the thyroid undergoes great enlargement, and the adrenals diminish in size. These organs are affected in a reverse order according as the food is deficient in certain essentials or excessively rich in other essentials. In the former case the adrenals enlarge and the thyroids diminish in size; in the latter the thyroids enlarge and the adrenals diminish in size.

The next picture represents a section of the normal thyroid gland of a pigeon. It is one of the control pigeons referred to on the previous chart. Contrast it with this one which shows a section of the thyroid gland of a pigeon that was fed on a diet of mixed grains and butter. You will notice that the vesicles are almost filled with acinar buds, and that there is epithelial hypertrophy and scanty colloid. You will recall that this picture is one which is commonly recognized as characteristic of Graves' disease. Here is another one. You will notice here also that the acinar budding and epithelial hypertrophy are extreme and that colloid is scanty or absent.

Now we come to the effect of adding onions to this diet of mixed grain and butter. The effect of the onions is to reduce the incidence of the thyroid enlargement, the size of the actual goitre, and to alter, to a considerable extent, the histological picture from a hypertrophic to a more vesicular type. There is a considerable degree of congestion; the cells are not so high; acinar budding is much less pronounced, and there is rather more colloid in the vesicles. Here is another section which shows the same appearances. It would seem, therefore, that the histological character of the goitres produced in consequence of confinement, lack of exercise, contamination of the food and drink by fecal material, and over-eating of food excessively rich in fats, is capable of variation dependent upon the composition of the food eaten. This question of the effect of onions is a very interesting one, and very difficult to explain. It may be that their protective action against the hyperplasia induced by the excess of fats is due to the iodine-content of the onions. That I do not know, but I understand that a very small amount of iodine is present in onions, while some samples have none at all. On the other hand, it may have been due to their content of diffusible antiseptic. This antiseptic, as you know, has a wide repute in the treatment of purulent bronchitis. Onions are used by the native doctors of India in the treatment of cholera, and *succus alii* has a wide utility in

Western medical practice. It may be, therefore, that this antiseptic action came into play in the present instance. It is certain that the addition of onions to a dietary of mixed grains and butter would tend to alter the bacterial flora of the gastro-intestinal tract. Possibly their beneficial action may have been due to such an alteration: or it may be that all three of the possibilities I have mentioned were concerned in bringing about the beneficial result.

The more I work on the problem of the factors concerned in the production of goitre the less disposed am I to tie myself down to any single influence in its production. So far as simple goitre is concerned we must in the present state of knowledge take count both of nutritional and bacterial factors in its causation.

The next step in this study of the effects of fats on the thyroid was to ascertain what component of the butter gave rise to the thyroid enlargement. To that end I fed pigeons on a diet of mixed grains and oleic acid. The experiment was controlled by feeding at the same time other pigeons on mixed grains and butter, and others on mixed grains and cod-liver oil. This experiment was designed with the object of putting the animals under hygienic conditions favorable to the development of goitre. Two pigeons were confined in each cage, so that the amount of movement was very limited, and the fecal pollution of their food-supply was extreme. In this picture I show you the result of the experiment, which lasted 130 days. First of all you will notice the effect which non-hygienic conditions of life—lack of exercise, close confinement, contamination of food and water-supply by the animals' excreta—have in causing the enlargement of the thyroid gland. You will observe also that the addition of cod-liver oil to the food affords complete protection against these influences. Mellanby has noted the same effect of cod-liver oil in dogs. Next you will observe the effect of butter and of oleic acid in causing enormous goitres, especially in certain cases. In the case of butter the largest pair of thyroids weighed 950 mg., while the normal weight is approximately 25 mg. Both thyroids weighed rather less than one four-hundredth part of the total weight of the animal. This effect was produced by butter; it was also produced by oleic acid. The goitres produced by oleic acid are even larger. In one case the two thyroids weighed 1,050 mg., or considerably more than one four-hundredth part of the total body weight of the animal; so that I think one may reasonably say that whatever effect butter has in causing hyperplasia can also be produced, and with equal certainty, by the unsaturated fat-oleic acid. It would, therefore, seem that the injurious effect of the butter is due to its content of this acid.

Now we come to another matter. I desired to pursue the question of the relation of fats to thyroid hypertrophy somewhat further, and to examine it from the point of view of fat-excess and iodine intake. For this purpose I used tadpoles, since their sensitiveness to the influence of iodine might serve as an index of the harmful effect exerted by fat-excess on the thyroid gland. The first thing that I did was to find a food on which tadpoles would grow and flourish, and to which the fats to be tested could be added. A mixture consisting of caseinogen, 15 parts, white flour, 85 parts, and green pond weed, was found to serve these purposes. The flour-caseinogen mixture could readily be made up into pills, either with water or with the fats to be tested. These pills were dropped into the china vessels containing the tadpoles and were readily eaten by them. In the case of the cod-liver oil they ate greedily at first and but sparingly later in the experiment. The charts which I now show you represent the results of this experiment. The addition of cod-liver oil, butter, or oleic acid to the basal diet caused great retardation in the rate of the growth of tadpoles. The same effect was observed with lard, cocoanut oil, linseed oil, and arachis oil. This experiment lasted fifty-five days, and the actual weight of twenty tadpoles was plotted week by week. The next step was to ascertain what effect iodine would have when added to the diets that were excessively rich in fats. This chart represents the control experiment and shows the rate of growth of tadpoles receiving neither fats nor iodine, and of those receiving 0.5 and 1 mg. of iodine respectively per 3 gms. of food-mixture without fats. The next represents the rate of growth of tadpoles fed on a mixture containing oleic acid. This dotted line represents the normal rate of growth in tadpoles receiving no oleic acid; the addition of 0.5 mg. of iodine almost completely compensated for the retardation of growth induced by the oleic acid, while 1 mg. of iodine did so completely. One mg. of iodine tended also to compensate for the retardation of growth induced by butter. In contradistinction to this compensatory action of iodine in the case of other fats, it will be noted that the addition of this amount of iodine did not compensate for the retardation of growth induced by cod-liver oil, but, indeed, further accentuated it. The more iodine one added to the cod-liver oil mixture the worse was the growth. I do not at the present moment wish to venture any explanation of these effects which, however, appear to be of much significance. It would almost seem that there is such a thing as a "fat-thyroid-iodine balance" and that a relative deficiency of iodine may be brought about in consequence of an excess of fat in the food and especially of the unsaturated oleic acid. If this be so it would provide an important example of a deficiency disease (goitre) due to want of one essential element of the food (iodine), resulting from excess of another essential food constituent (fat).

I have shown you the effects of deficient foods on the thyroids and adrenals of pigeons; it remains now to show the effects of deficient foods on animals more closely related to man. This chart shows the results of such foods as observed in monkeys. This column represents the normal weight of the adrenal glands in control monkeys; a diet which is deficient in all vitamins causes enlargement of the adrenal glands just as it does in pigeons. The thyroid atrophies, and there is a tendency to enlargement of the pituitary body, especially in males, just as there was in pigeons.

The next picture represents a cross-section of the adrenal gland of a healthy pigeon stained by osmic acid. It shows the normal proportion between the cortical and the medullary columns. The slide shows that in pigeons subjected to complete avitaminosis the cortical areas are greatly increased in consequence of the deficient food. There is at the same time a depletion of the cortical lipoids, as demonstrated by Cramer. I have shown that an increase in the epinephrine content approximately proportionate to the increase in size of the glands occurs. This effect on the epinephrine content is seen in the blood pressure tracings from sheep. The next specimen is a section of a sympathetic ganglion attached to the suprarenal gland of birds. I show it to you in order to point out the degenerative changes that take place in the nerve cells of the ganglion in consequence of avitaminosis.

I find, gentlemen, that I have been talking for well over an hour, and that is quite long enough. I hope I have not kept you too long. It was by request that I inflicted the historical survey of my earlier work upon you, and as for my recent results I lay them before you so that you may for yourselves form your own opinion in regard to them. I have thought it best to present the facts as I observed them, and to refrain from attempting to interpret them, for, indeed, much work still remains to be done before their true significance can be appraised.

Discussion

Dr. Marine: I really had not planned to say anything, but as Colonel McCarrison has been unkind enough to mention my name a number of times in connection with this work, I suppose I shall have to. It has been a great opportunity to hear a man talk who has really seen goiter. Most of us have never seen it. I have lived in the Lake basin about sixteen years, and I saw goiter there, but nothing remotely approaching what Colonel McCarrison has seen in the Himalayas. Truly that must be the most severe goiter district in the world.

I was interested in what Colonel McCarrison said about the morphology of the thyroid. Of course a great deal is written and heard about this, but I had hoped that medicine was over the stage of spending a great deal of time on the morphological variations in the thyroid. It is such a labile tissue that it may undergo morphological changes within twenty-four hours. It seems to me quite as labile as the blood tissue. To say that this change is typical of this disease, and that change of that disease I think is quite impossible, and I believe, although I have very few friends in that regard, that there are more people coming to that point of view.

Another thing which I did not know about before is that the incidence of endemic goiter in India bears no relation to the incidence of Graves' disease. In this country it does seem to bear a relation in a great many cases. Colonel McCarrison's explanation that Graves' disease is a disease of civilization is one that appeals to me. Both Graves' disease and simple goiter are increased in the Great Lakes district of our country. In the negro one rarely sees exophthalmic goiter. I have seen several cases of it in mulattos. Colonel McCarrison's statement is interesting that Graves' disease is very rare in the natives in India, but may develop in those same natives when transported to the war zone.

The question of adenomas, the so-called toxic adenoma, is a very interesting subject. I have the feeling that the adenoma is of secondary etiological importance in the development of this peculiar syndrome or toxic picture. My experience has been somewhat similar to what Colonel McCarrison saw in India, that most endemic goiters eventually develop adenomas, and yet the incidence of toxic adenoma is exceedingly small. It seems to me that Graves' disease or toxic adenoma must be something more than the mere presence of an adenoma. That is the personal feeling I have.

Regarding the etiology of goiter, and with all due deference, I do not believe that water is the etiological factor. If water is related to goiter I believe it is due to the absence rather than the presence of something in it. On the other hand, the investigations which Colonel McCarrison has carried on with bacterial toxins seem significant to me, and there is no doubt there is some association when we remember that in infectious diseases the thyroid usually reacts. Why or how I cannot explain.

Another important point in the paper to-night is the observation that in inanition and in deficiency diseases in general the cortex of the suprarenal gland may undergo a most remarkable enlargement. That is a striking thing, but that is not all of it. The epinephrine content likewise is increased. I might digress just a moment to mention some recent work with the adrenal cortex. I have shown that if you cripple the adrenal cortex in a cat or a rabbit there is a remarkable increase in heat production which may last for months. That increase in heat production is associated with increased activity of the thyroid gland. If the thyroid gland is removed, and then the suprarenal cortex is crippled, you will not get increased heat production. There is some relation then between the suprarenal cortex and the thyroid gland which is a relatively new thing as compared with the older relation between the chromaphil system and the thyroid gland. In other words, epinephrine will stimulate the thyroid gland. I think Dr. Goetsch will accept that. If we have shown anything it is that the suprarenal cortex also plays a rôle in thyroid activity.

The last point brought out was really quite new to me until recently, that is, the relation of fat feeding to the histological evidence of thyroid activity. Looking back over the work I have done in the last sixteen years it seems to me that I can see confirmation of Colonel McCarrison's results. In fish, for example, brook trout would get goiter when fed with pigs' liver. I have seen chicken farms that had to be abandoned because of goiter. I have seen several dairy herds in the Lake region where nearly all the calves were cretins with huge thyroid enlargements and these were fed with cotton-seed meal in large quantities. All these facts further indicate that there is something in the observation. How it operates is what I would like to ask Colonel McCarrison, but he has forestalled that question by saying that he has no idea.

Colonel McCarrison has stated that oleic acid is very potent in producing thyroid hyperplasia, but that the administration of iodine with it markedly decreased this effect of oleic acid. I would like to ask one question. Have you worked with a series of fatty acids from the completely saturated fatty acids through oleic on to those very unsaturated fatty acids? I would like to know the effect of iodine in relation to the degrees of unsaturation. This is all a very interesting question, and we have no idea what it may be due to. It may have something to do with thyroid function and with alterations in suprarenal function, and after all we are trying to develop some of these interrelationships. Many people think it is very simple—that all you have to do is to put a few animals in a cage, use a little imagination, and a new relationship is established. I would like to put in a protest against what I am pleased to call "Endocriminology," because I do think it is criminal that a subject with such great possibilities should be exploited both commercially and scientifically.

Dr. Goetsch: I want to express my thanks to Colonel McCarrison and assure him of the great interest I had in listening to his presentation. I am not in a position to discuss his paper because my experiences are not as a rule with the simple goiters. These very rarely come to the surgeon, and my work is almost entirely with goiters producing hyperthyroidism. I was particularly interested in what Colonel McCarrison said about the occurrence of adenoma in India, and its percentage as compared with this very large number of simple goiters. I have always felt that the adenoma had no relationship to the same etiological factors on which simple goiter seems to depend, because of the fact that adenoma is a new growth. It is a benign growth. It is always encapsulated, and if it is not encapsulated it is not an adenoma. Until we know what the cause of tumors is, we cannot say anything about the cause of adenoma. Then too the adenoma as far as I know has not been influenced greatly by any form of treatment with which I am familiar. The adenomas which I have seen are those which are causing hyperthyroidism. On a histological basis I think we have reason to say that the adenoma is responsible for hyperthyroidism of itself, because if you submit them to a very careful study for the presence of mitochondria, you will find that in every case of an adenoma associated with hyperthyroidism, the cells are rich in mitochondria. These mitochondria are excessively abundant, and if a section is taken from the thyroid gland just beyond the capsule of the adenoma, one finds that the thyroid gland itself has a colloid structure, in which one finds very few or no mitochondria at all. I have taken an adenoma from the side involved, and a wedge of tissue out of the opposite thyroid lobe in which one finds the same picture, and it seems to me that the cells of the adenoma, showing thus histological activity, are responsible for the hyperthyroidism present. I have tried to explain this colloid change in the gland outside of the adenoma on the same basis that Dr. Marine has caused the thyroid hyperplasia in his animals to revert to a simple colloid picture following the administration of iodine. I believe that the adenoma furnishes a toxic body which is closely related to thyrotoxin, and which is present in the body fluids in excessive amounts, and that the normal thyroid as a consequence reverts to a simple colloid picture very different from that seen in the adenoma. I have felt that if we were able to go back into these individuals after the excision of an adenoma we would probably find that this resting thyroid which before had a very simple inactive looking picture with the absence of mitochondria and the presence of fat would again take on an active appearance. In a simple colloid goiter the cells are filled with fat, and there is the absence of mitochondria. After the excision of the adenoma I believe this resting thyroid comes back to the normal picture again. I do not quite understand what Dr. Marine meant by saying that these simple colloid goiters might develop through all stages to the formation of adenoma and finally fetal adenoma. I do not know whether you meant the formation of these encapsulated tumors that have no relation to the thyroid as such, that can always be shelled out, or whether you meant those hyperplastic more or less circumscribed areas which one often sees.

Dr. Marine: I was speaking of all degrees of encapsulation.

Dr. Goetsch: These adenomas always have a definite capsular structure separating them from the normal thyroid, and one can see even microscopic adenomas, and from them trace their evolution up to those large ones with a capsule one centimeter thick. That is the adenoma I meet in my work. Of course those adenomas that do not produce symptoms of hyperthyroidism will not come to the surgeon for treatment, except when they produce symptoms of pressure.

Colonel McCarrison: Do you see a constant type?

Dr. Goetsch: We get every possible microscopic picture in adenoma, and I feel that being a tumor and arising from the fetal cells of the thyroid, it has the potentiality of developing into any histological type from the simple colloid to the higher degrees of hyperplasia resembling that seen in exophthalmic goiter. The fact that these fetal cells can reproduce any type of histological picture makes it very confusing and difficult to classify the adenomas. But when one applies the technique for the demonstration of mitochondria, then one finds that the simple adenoma without symptoms is relatively poor in mitochondria, and that the toxic adenoma, associated with definite symptoms of hyperthyroidism, is just as rich in these structures as exophthalmic goiter. If one applies the criterion of mitochondria one need not care whether the cells are tall or not, or whether there is much or little infolding. The presence or absence of mitochondria forms a better criterion of activity. In exophthalmic goiter the mitochondria are always present in large numbers. I have never had a case in which I have failed to find them. I have examined between three or four hundred. The adenomas are much more common of course.

Dr. Ewing: A countryman of Colonel McCarrison's said some time ago that medicine had passed beyond the descriptive stage, and was now engaged in quantitative measurements of the phenomena of disease. That may be true in certain very well known diseases, but we are still in the descriptive stage in thyroid diseases, and the observations which Colonel McCarrison has made illustrate the type of work by which successful research in this field may be conducted. I am greatly impressed by the ingenuity with which he carried on his work away out in northern India. It shows that when one has the idea and the will the environment will lend itself. In regard to the practical aspects of this matter, I am extremely interested in the experiments with the thyroid and the adrenal, because they give one a new point of view from which to carry on work as a general pathologist. I have been looking at the adrenal for a good many years, without much intelligence, I must confess. We are getting information about the adrenal lately, and I find it possible to use a little more intelligence in the examination of this and the other endocrine glands at autopsy. I think in this way we are eventually going to get a basis on which to build up endocrinology and bring actual scientific facts to bear on many of these problems. I think the general pathologist has a function to perform here, so I want to thank Colonel McCarrison again and trust that his work will reach the fullest fruition.

Dr. Pappenheimer: It was not clear to me whether this hyperplasia of the adrenals is due to a specific deficiency of the accessory substances, or is merely an accompaniment of the wasting that one gets under those circumstances. Have you made any experiments in which the vitamine deficiencies were supplied but in which the total food intake was insufficient? I should like to ask in this connection whether the cortical hyperplasia is due to a passive overloading of the cortex with lipoids mobilized during the process of acute inanition?

Dr. Oppenheimer: I should like to ask what is the geology of that district in India and just what is the history of the neighborhood.

Colonel McCarrison: I do not propose to say much by way of reply except to answer the questions that have been put to me so far as I can.

As to the matter of the specific action of vitamins on the adrenal glands: An increase of the epinephrine content occurs in consequence of inanition. An increase of the epinephrine content occurs also in consequence of complete avitaminosis. No increase in epinephrine content appears to occur if vitamin A be supplied in the food. Associated with the hypertrophy of the cortex that results from avitaminosis, and coincident with the increased epinephrine content in the medulla, a depletion of the cortical lipoids occurs. Cramer has shown that the depletion of lipoids from the cortex is associated with the absence of vitamin A from the dietary. The absence of vitamin C produces some very curious effects. In guinea pigs fed on a scorbutic diet the adrenals are greatly enlarged; circumscribed areas of hemorrhage also occur in the cortex. I have never seen precisely this appearance in any other condition. The circumscribed areas of hemorrhage are distributed all around the adrenal cortex. The absence of vitamin A is associated with a great fall in the epinephrine content. The adrenal changes are among the earliest of the manifestations of vitamin C deficiency.

In regard to the question about the geology of the Gilgit district, I regret that I cannot rely on my memory at the moment for details regarding it. An account of its geology was kindly prepared for me by an eminent geologist who visited the district, and the matter is dealt with in my Milroy Lectures delivered before the College of Physicians of London in 1913. I would refer you, sir, to the original source for the answer to your question

TUMORS (3) OF THE KIDNEY PELVIS AND OF THE URETER

P. W. ASCHNER, M.D.

We are all familiar with the ordinary papillary tumors of the bladder, and with the usual types of carcinoma of the bladder, but we are not so familiar with, and do not see so often, these types of tumors in the kidney pelvis and in the ureter proper. Within the last year we have had three such cases.

The first of these was a man of fifty with hematuria, who on cystoscopy showed a very small papilloma at the neck of the bladder, which was destroyed by fulguration. However his bleeding continued, and another cystoscopy showed blood coming down from the left kidney. Nephrectomy was contemplated, but the man had a cerebral accident just before operation, and died. At autopsy the specimen was removed. It was a large kidney, the upper half of the pelvis showing a diffuse papillary growth, not of great thickness, not invading the kidney parenchyma, nor the submucous tissues. On section it proved to be an apparently benign papillomatosis of the renal pelvis. The other kidney was found to be extremely small and insufficient in tissue, so that had the contemplated nephrectomy been done the patient would probably not have survived.

The second case was another of left-sided hematuria in a man of sixty-two whose kidney was explored, and at operation was found to be a small and apparently nephritic one. Decapsulation only was done. A year and a half later, owing to the recurrence of the hematuria, he was again cystoscoped, and sticking out of the mouth of the left ureter was a small papilloma. We concluded that this was an implantation growth, the primary one presumably being in the renal pelvis. The kidney and ureter were removed The kidney contained in its pelvis a large tumor occupying the greater portion of the pelvis and its calices and invading the kidney parenchyma at the upper pole, with a number of small implantations along the course of the ureter. On microscopic section it proved to be a papillary carcinoma.

The third specimen is one from a man who had the typical history and signs of calculus disease of the right kidney. At operation a pyelotomy was done and the stones removed from the pelvis. At the site of the ureteropelvic junction a stricture was encountered. Because of the thickness of the tissue a small specimen was removed. We were much surprised to find that this was a squamous-celled carcinoma, primary in the ureter. The kidney and ureter were removed at a secondary operation immediately after the diagnosis was made. In addition to the ureter lesion, he had a very interesting condition. It was leukoplakia of the pelvis, chiefly in the lower of the two pelves which the kidney presented. The man has been well since except that he has the leukoplakia in the bladder. The association of leukoplakia with cancer is well known in the tongue and the bladder, and I have looked through the literature and found no case of leukoplakia associated with carcinoma in the ureter. I am not convinced that it is on a leukoplakic basis *per se*. The ureter itself does not show a leukoplakic condition, and it is conceivable that he had a stricture at this point in his ureter, and that some of the leukoplakic material passed from the pelvis of the kidney, became caught at this point, and developed into a carcinoma.

I present these as three rather interesting unusual kidney tumors. It is interesting that fragments of the pelvic tumors are apt to break off and implant themselves in the ureter or the bladder. Such a growth in the bladder misleads one into believing that the bladder tumor is the cause of the hematuria. The case of squamous-celled carcinoma of the ureter is exceedingly rare. I have found only three in the literature, and of all primary tumors of the ureter, there are only about fifty on record.

Discussion:

Dr MacNeal: I think it is a very interesting suggestion, made apparently without reservation, that secondary tumors arise in the ureter and in the bladder by implantation after transportation through the urine itself of particles of primary tumor from the pelvis of the kidney. The proof that implantation takes place in such a manner is rather difficult to furnish. I am not sure that it is generally accepted that this does occur. One has to think of other possibilities; there may have been perhaps a simultaneous development of tumors of the same type in various portions of the urinary tract. Also, one should perhaps think that the tumor may have metastasized through the lymph stream rather than through the lumen of the ureter itself. It is difficult to decide between these possibilities. The question of the implantation of tumors, especially the implantation of malignant tumors, or their metastasis by other routes than through the blood or lymph stream or by immediate contiguity, is unsettled in pathology.

Recently we have seen a case in which papilloma of the pelvis of one kidney was present and this was removed. Some months later the patient returned and had a papilloma removed from the rectum. There was a difference of opinion between the surgeons in this case as to whether the papilloma of the rectum might not be regarded as in some way derived from the papilloma in the kidney pelvis. The histology of the second specimen was that of the usual papilloma which occurs in the rectum, and it did not resemble that in the kidney pelvis.

The tendencies which exist in epithelial surfaces to develop papillary tumors have to be recognized as a tendency which may be common to a considerable surface of the epithelium, and the question as to whether the second tumor is an implantation of the first is a question about which we should keep an open mind in the present state of our knowledge.

DR. ASCHNER: The points made are very pertinent. We have a certain amount of clinical as well as pathological evidence that papillomata, particularly in the genito-urinary tract and probably in other parts of the body, can arise by implantation not through the lymphatics and blood stream. To my mind it is inconceivable that a papillary tumor at the neck of the bladder can come from the pelvis of the kidney by the lymphatics, because the lymphatic stream is in the other direction. I doubt if it would arise through the blood stream, because these tumors are very superficial things. It is not a malignant tumor in the sense of spreading by metastasis, but it can spread by implantation. In papillomatosis of the bladder that is true. You may observe a papilloma in the bladder near the ureter orifice and some time later see another at the fundus of the bladder. That is called a "kissing" lesion, for when the bladder is empty the fundus meets the trigone. The same thing is seen in tuberculosis of the bladder. We know that a bladder papilloma may be operated on, and all the tumors apparently removed; if the greatest precaution is not taken the patient may develop a growth in the suprapubic wound and along the course of the incision made in the bladder at the time of operation. That is one of the reasons why we cauterize the line of incision after the operation. I think these facts offer considerable evidence to show that papillary tumors of this type can implant themselves.

ANEURYSM OF THE HEPATIC ARTERY

WILLIAM FRIEDMAN, M.D.

(*From the Pathological Laboratory of Mount Sinai Hospital, New York City*)

The patient, 57 years old, born in Russia, house-wife, was admitted to Mount Sinai Hospital on the service of Dr. A. V. Moschcowitz on July 16, 1921, with the following history:

Seven years ago she was operated upon for gall-stones at the Beth Israel Hospital. A cholecystectomy was done and the patient had an uneventful recovery. Six years ago she had an attack of severe colicky pain in the epigastrium radiating into the back and accompanied by vomiting which lasted for several days. During the week previous to her admission she had again suffered severe colicky pain in the epigastrium which radiated to the back. She had several such attacks during the week. Most of the attacks were accompanied by vomiting. Twenty-four hours before admission the patient noticed that she had become jaundiced. The only other important symptom in the history was nocturia for six weeks previous to admission.

The physical examination revealed an obese middle-aged woman, intensely icteric and acutely ill. There was marked tenderness and rigidity over the entire right side of the abdomen, especially in the right upper quadrant, but no rebound tenderness. The liver was palpable 4 cm. below the costal margin on the right side. The edge was sharp, the surface smooth. There was a moderate leucocytosis and secondary anemia. The stool contained blood, but no bile. Blood Wassermann was negative. The blood chemistry showed urea nitrogen 50, incoagulable nitrogen 100. Her temperature varied between 99 and 104 and the pulse between 96 and 100. Respirations were 24.

Two days after admission the patient passed a large stool consisting entirely of old fluid and clotted blood. Her condition became worse and operation was decided upon. The operation was performed by Dr. Aschner. The omentum and transverse colon were found densely adherent to the abdominal wall and under surface of the liver. The intestines were plum colored. The common bile duct was found markedly dilated and when aspirated yielded a small amount of blood. Upon opening it several large blood clots were found. The right hepatic duct was probed and found free. The left hepatic duct when probed yielded profuse bleeding. Some obstruction was met in probing the common duct toward the papilla. A duodenotomy showed the papilla to be normal and a probe could be freely passed into the common duct. The surface of the liver showed no irregularities. A tentative diagnosis of carcinoma of the left hepatic duct was made. The patient died several hours after the operation.

Autopsy revealed a most intensely icteric middle-aged woman. The heart showed some irregular atherosclerotic thickening of the mitral cusps. There was also marked atherosclerosis of the aorta. The peritoneal cavity contained no free fluid. The liver weighed 1,830 gm. The gallbladder was missing, having been removed at a previous operation. On probing the right and left hepatic ducts a large amount of clotted and fluid blood exuded. Just posterior to the right hepatic duct was found a spherical aneurysm about 0.75 cm. in diameter. The aneurysmal sac was filled with an organizing thrombus which protruded through a defect in the right hepatic duct. The common and hepatic ducts and their smaller radicals were distended with blood throughout the entire liver. The intestines contained a great deal of old blood. Microscopically the hepatic artery and all its branches showed marked atherosclerotic changes. There was found a generalized atherosclerosis throughout all the medium-sized systemic arteries which were examined.

Up to June, 1921, there were fifty-four cases of hepatic artery aneurysm reported. The disease is more common in males. Grunert believes 75 per cent. followed acute infections. Rolland is of the opinion that as high as 20 per cent. are due to syphilis. Among other etiological factors are gallstones, and trauma at operation. There are two varieties: extra-hepatic and intrahepatic, the former being more common. It occurs most often in the main branch of the hepatic artery. They may be multiple.

Hoeglar believes that 50 per cent. of the aneurysms are mycotic in origin. Usually the vessels in the liver show thickening of the intima and media. Ledieu reported one case in which there was healing of the aneurysm. Death is usually due to rupture of the aneurysm into the peritoneal cavity, the biliary passages, the stomach or the duodenum. The pressure of the aneurysm on the biliary ducts is supposed to be the cause of jaundice.

In view of the history of this case, of an operation for gallstones seven years previously which was followed a year later by a severe attack of abdominal pain similar to the one which initiated the patient's final illness, the possibility must be considered that the aneurysm was due to weakening of the vessel wall as a result of trauma or of infection at the time of the operation. In view of the extensive general atherosclerosis throughout the body, in which the hepatic artery had proportionately shared, a weakening of the wall as a result of this process must also be considered. Investigation has revealed that there was no unusual trauma or infection at the time of operation and it would, therefore, seem that the aneurysm of the hepatic artery was due to an atherosclerotic change within the artery with subsequent rupture of this aneurysm into the right hepatic duct and death due to hemorrhage.

Discussion:

Dr. G. A. Friedman: I was very much interested in the case of Dr. W Friedman and in his excellent presentation of it. I would like to mention that about nine years ago I had a case in which I made a tentative diagnosis of aneurysm of the hepatic artery. A report of the case with operative findings was published at the time. I shall refer to the history later. The patient was operated upon by Dr. Arpad Gerster, April 9, 1912. These were the findings at the operation: "As soon as the margin of the lesser omentum was exposed, the artery became visible as a pulsating cylindrical body, having the diameter of a large goosequill. It formed a loop with its convexity downward. Its proximal continuation could be distinctly followed by palpation of the celiac axis, this forming a large loop with its convexity pointing upward, so that the whole vessel, as far as visible and palpable, represented a large Roman 'S,' its entire estimated length being six inches. A marked whirl could be felt on the gentlest contact with the vessel. The gallbladder was normal, moderately distended with bile, easily expressed into the common duct. The common duct was not distended and contained no stones, no palpable tumor, no cicatricial ulcer, absence of stone in the gallbladder.

"All the exposed structures, especially the duodenum, showed marked cyanosis charged to the bad anesthesia. The margin of the liver was markedly rounded and thickened, free from cicatrices. The stomach was much dilated by gases which were withdrawn with a tube. The index finger could be easily invaginated into the pylorus." The division of the aorta into the iliacs instead of corresponding to the fourth corresponded to the second lumbar vertebra. The calibre of the aorta and iliacs and the coronaries of the stomach was normal. "Diagnosis—Dilation and elongation of the hepatic artery. No aneurysm." I quoted in my paper Kaufmann, who says: "Dilation of an artery, also called arteriectasia, may be diffuse or circumscribed. Some authors call only the latter aneurysm, but this is in an error; there are transitions between the two forms."

Dr. Gerster himself called my attention several months later to an article which appeared in a journal, edited by Professor Gare, in which my case was quoted as follows:

"In a woman of about thirty-five years old, who gave a history of excessive use of alcohol, the following symptoms were noted: severe paroxysmal pain in the right hypochondrium which became more intense in prone position, visible pulsation over the region of the liver, a subjective sensation of throbbing in this area. Lower border of liver was palpable. Diseases like gallstones, duodenal ulcer, tumor, visceral arteriosclerosis, cirrhosis of the liver, aneurysm of the aorta were ruled out. A diagnosis of aneurysm of the hepatic artery was made and the diagnosis was confirmed through exploratory laparotomy."

Three years later Professor Alb. Narath of Heidelberg, in discussing in his paper the necessity of ligating the hepatic artery in aneurysm, refers to my case as follows: "What happened in Friedman's case should never occur again. One should not satisfy himself with an exploratory incision in this condition, simply leaving the patient to his fate." I believe therefore that my case was an aneurysm of the hepatic artery. What became of my patient I do not know. I saw her seven months after her operation: her complaints and the clinical picture remained practically the same as before the incision.

In concluding I would like to say a few words in regard to Dr. W. Friedman's paper. It is possible that his patient had already her aneurysm at the time when she was operated upon at The Beth Israel Hospital for gallstones, because in the literature cases are recorded in which gallstones and aneurysm of the hepatic artery were found simultaneously. That the latter condition has a chronic course, over a period of years, is known to anyone who has looked up the literature of the subject.

Dr. Rosenthal: Were the other vessels in the case of Dr. William Friedman investigated in reference to periarteritis nodosa?

Dr. William Friedman: The vessels were investigated with that in view. Teacher and Jack about a year ago published a case of hepatic artery aneurysm and reported a lesion which looked very similar to the lesion found in periarteritis nodosa. In this case we found no such lesion.

CALCIFICATION OF THE PERICARDIUM

A. WINKELSTEIN, M.D.

(*From the Pathological Laboratory, Mount Sinai Hospital, New York City*)

The specimen is the heart and the pericardial sac from a male patient 39 years old who was admitted to Mount Sinai Hospital in June, 1921. Ten years before, following an attack of rheumatic pain in the left arm, he was admitted to the Presbyterian Hospital with cardiac symptoms—chiefly dyspnea, palpitation, and edema of the lower extremities. He recovered in eight weeks and remained without symptoms until three years later, when he had a similar attack lasting five weeks. Following this he was well until two months before admission to Mount Sinai Hospital. His complaints then were dyspnea, cough, anorexia, weakness, epigastric pain, and edema of the lower extremities. The physical examination pointed to a cardiac decompensation due to aortic stenosis and mitral stenosis with insufficiency. Furthermore, on account of a continuous fever, irregular chills, and the occurrence of numerous white-centered petechiæ in both conjunctivæ and in the skin generally, an active subacute bacterial endocarditis was suspected. Four blood cultures, however, were negative. A broncho-pneumonia was also present. Three weeks later he went into a stupor and died. Briefly then, this case was one of cardiac insufficiency probably due to rheumatic valvular defects and possibly complicated by an active subacute bacterial endocarditis.

The post-mortem findings were very interesting. There was bronchopneumonia, old right pleural adhesions, and an enlarged, granular liver, showing microscopically perilobular cirrhosis, and chronic passive congestion of the spleen, kidneys, and intestines. The coronary arteries and aorta were negative. The pericardium was universally adherent to the surrounding structures.

The heart with the pericardium weighs 1,100 gm. and appears like a huge cor bovinum. The visceral and parietal layers of the pericardium are universally adherent and thickened. In the region of the atrio-ventricular grooves the thickening amounts to several centimeters. Here it is densely infiltrated with lime so that a bony hard ring almost completely encircles the heart. This calcification extends for a distance of a few centimeters down on both ventricles and up on both auricles. On cracking open this ring small cavities are found in some places which are filled with cheesy, caseous material or thick pus. Both auricles are tremendously thickened and dilated. There is a moderate hypertrophy and dilatation of the right ventricle and a huge hypertrophy and dilatation of the left ventricle, the myocardium here measuring 3.5 cm. in thickness. There is a moderate stenosis of the tricuspid valve due to thickening and fusion of the cusps and a very marked mitral stenosis, the aperture of the valve admitting only the tip of one finger. The bases of the mitral valve cusps are infiltrated with lime. On the auricular aspect of the mitral valve, there are two irregular fissures covered with blood platelet thrombus (the probable source of the petechiæ). The aortic cusps are so thickened, fused, and infiltrated with lime, as to form a moderate degree of stenosis as well as insufficiency. The myocardium is normal in color and presents grayish streaking.

The radiograph of the excised heart and pericardium reveals the calcification so exquisitely as to give one a false impression of overlying ribs.

Microscopically the pericardium shows a thick layer of scar tissue in some places and marked deposition of lime in others. Also within the calcified areas, scattered here and there, small areas of bone formation are found. There are also large areas of purulent infiltration which have a tendency to invade the myocardium. No tubercles are seen. The heart muscle is markedly hypertrophied and there is a moderate amount of perivascular and interstitial fibrosis. Bacteriologically, smears, cultures, guinea pig inoculation from the pus and tissue stains for the usual bacteria and for tubercle bacilli all proved negative.

Summarizing, the specimen shows:

1. A universal pericarditis externa.
2. An extensive adherence of the visceral to the parietal pericardium.
3. The presence of an old suppurative pericarditis with marked calcification and some ossification occurring chiefly in the atrio-ventricular region.
4. A tricuspid and mitral stenosis—an aortic stenosis and insufficiency.
5. Myocardial hypertrophy and dilatation.
6. A negative bacteriological study.

From the clinical and pathological findings in this case it seems fair to conclude, although this cannot be proved, that this man had, in the course of his ten years' illness, (1) an acute rheumatic fever, (2) rheumatic endocarditis resulting in his valvular defects, and (3) a complicating suppurative pericarditis with subsequent calcification and ossification, the exact etiological agent of the pericarditis being unknown.

On account of the rarity of such calcification and ossification and the unusual nature of the specimen it seems worth while to attempt to summarize briefly the available literature on the subject. Fritz Diemer in the *Zeitschrift für Heilkunde* first drew attention to this condition, describing in 1899 ten cases. In 1901 A. E. Jones in the *Transactions of the Pathological Society of London* collected and analyzed fifty-eight cases occurring in the literature from 1726 to 1897. In 1902 H. I. Wells reported four cases from Cook County Hospital. Simmonds of Hamburg reported in 1908 the X-ray diagnosis of such cases during life, and in 1918 his assistant, E. F. Müller, added eight cases with a splendid critical discussion. These are the outstanding papers on the subject. The following points in these papers are of interest.

It is a very rare disease. Up to the present there are only seventy-five cases on record. It occurs three times more frequently in men than in women, and the age varies from twenty-nine to sixty-six years. The etiological agent in some cases was definitely the tubercle bacillus, in one case the anhemolytic streptococcus and, in another, old hemorrhage; occasionally a preceding rheumatic fever or pericarditis is mentioned. In fully two-thirds of the cases, however, the cause was not demonstrable.

The pathogenesis in these cases is not entirely clear. As you know, the course of a pericarditis is determined by the virulence and character of the infecting agent, the resistance of the individual, and the therapy applied. Depending on these factors one will find the outcome to be either (1) death of the patient or (2) complete restoration to normal or (3) more or less thickening of the pericardium or (4) adhesions—complete or incomplete—internal, external, or both, or (5) inspissated pus or blood or caseous masses—loculated or not. It is chiefly in such purulent, hemorrhagic, or caseous areas that lime deposition occurs. It occurs also occasionally in large areas of scar tissue or adhesions. Although the exact physico-chemical factors involved in calcification are not yet completely known, it is a general rule that wherever there are large areas of dead, dying, or hyalinized tissue, lime salts may be deposited.

One finds the following pathological features in these cases: (1) frequently a pericarditis externa, (2) an adherent pericardium—usually universal, and (3) calcification. This calcification is variously described in the form of granules or masses; plates in or between the visceral and parietal pericardium; irregular pieces extending into the myocardium; rings or bands (especially in the atrio-ventricular grooves), and rarely there is a complete enclosure or the so-called "cuirassed heart sometimes designated as the marble heart." A few cases are described where the calcification proceeds outward from the bases of the valves. Very rarely, as in the case reported here, a partial ossification in the calcific areas may occur. The other organs often show changes. The heart may be hypertrophied and dilated—pleural adhesions are frequent and cirrhosis of the liver is mentioned in one-seventh of the cases.

Muller brings out the following points in the study of his eight cases: (1) The process nearly always commences in the pericardium over the right ventricle. (2) It is progressive. (3) It later extends to the left heart. (4) The cause is subacute and acts for a long period of time. (5) The tubercle bacillus and the anhemolytic streptococcus could act in such a manner, he supposes.

There is no definite clinical picture of this disease. In 25 per cent. of the cases there were no symptoms and in the others merely those of cardiac insufficiency. Although metallic murmurs and osteal percussion notes have been described, these seem to have been post-mortem retrospects. In 1908, Simmonds at Hamburg made the important observation that extensive calcification of valves, myocardium, or pericardium could be diagnosed during life by the X-ray. Since then Groedel, Schwartz, Weill, and Rieder have reported cases so diagnosed. Obviously, however, the diagnosis is only of importance in regard to the prognosis, since treatment is of no avail.

Discussion:

DR. ST. GEORGE: We had a case of calcification of the pericardium recently in Bellevue following an empyema which the patient had, and was operated for. The calcium deposited in the pericardium was torn during the attempted operative removal in such a way that it ruptured into the auricle and the patient bled to death. In this case the individual had no lesion anywhere in the endocardium. All the valves were normal. He had an adhesive pericarditis with this calcification which involved the pericardium on the side in which the empyema was, and also along the diaphragmatic surface.

There was no evidence of bone formation in this calcium.

Bibliography.

F. DIEMER. *Ztschr. f. Heilk.*, 1899. xx S., 247.
A. E. JONES. *Trans. Path. Soc. London*, 1901, lii, 181.
H. I. WELLS. *Amer. Jour. Med. Sc.*, 1902, cxxiii, 241.
E. F. MULLER. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1918, xxv, 231.
SIMMONDS. *Fortschr. a. d. Geb. d. Rontgenstrahlen*, xx S., 371.

1. MULTILOCULAR ECHINOCOCCUS OF THE LIVER
2. HYDATID ECHINOCOCCUS OF THE SPLEEN

LEO EDELMAN, M.D.

(*From the Pathological Laboratory of the Mount Sinai Hospital, New York*)

The specimens which I have to present before the Society illustrate the two types of echinococcus found in man,—one, a multilocular or alveolar echinococcus of the liver and the other, shown mainly by way of contrast, a hydatid echinococcus of the spleen.

The first specimen was removed from a Russian woman, age 33, admitted to the surgical service of Dr. Berg, May, 1918. She entered the hospital complaining of pain, tenderness and discomfort in the right upper abdomen which had been present for about two months. There was no radiation of pain and no jaundice. In her past history she related that a mass was felt in that region by her family physician some two years before onset of symptoms but she declined operation at that time. This mass grew very slowly and only became tender a few weeks prior to admission to the hospital. On physical examination the patient appeared slightly emaciated, and presented a palpable mass just below the costal margin in the right upper abdomen which felt firm, nodular, and was freely movable with respiration, apparently attached to the liver. The blood picture and blood Wassermann were negative, as was the X-ray.

The patient was operated upon by Dr. Berg, who found a hard nodular mass intimately connected with the liver and overlying an apparently normal gallbladder. In the absence of any palpable metastases, he considered the condition a primary operable carcinoma of the liver and resected the tumor.

The excised specimen which was sent to the laboratory consisted of an irregular yellowish white, rather firm, nodular tumor mass measuring about 10 x 8 cm., roughly triangular on cross section with normal liver tissue at the base of the triangle. To the outer aspect of the mass, attached partly to it and partly to the liver tissue, was an apparently normal gallbladder. The cross section through the tumor presented a honeycomb appearance, the spaces containing cholesterin-like material with granular detritus simulating necrosis. The gross appearance of the tumor suggested the following possibilities: (*a*) Gumma of the liver; (*b*) Colloid carcinoma with ulceration and necrosis; (*c*) Multilocular echinococcus.

Under the microscope the diagnosis of multilocular echinococcus disease of the liver was established, although no hooklets were found. The stroma defining the characteristic alveolar spaces consists mainly of sclerosed connective tissue derived from the liver, granular detritus with remnants of degenerated liver cells, leucocytic infiltration (round cell and polymorphonuclear) near the periphery, and alveoli containing greatly contorted and folded chitinous vesicles filled with plugs of colloid material. Some areas show caseation and coagulation necrosis resembling a gumma or solitary tubercle with perivascular infiltration.

The patient made an uneventful post-operative recovery and was lost track of after leaving the hospital.

The second specimen was removed from a young woman, age 26, a native of Poland, admitted to the surgical service of Dr. Elsberg, September, 1921. She entered the hospital complaining of discomfort in her left upper abdomen which had existed for about ten days. Nothing abnormal was detected by her family physician prior to this time. Her previous history was negative. On physical examination the patient appeared moderately well developed and presented a rather firm fixed mass in the left upper abdomen, which reached downward to the level of the umbilicus and across to the mid-line. The liver was not palpable. There was no jaundice. The blood picture and blood Wassermann were negative. The temperature was normal, and urine negative. X-ray of pneumoperitoneum (Oxygen) showed an enlarged spleen and small liver.

The patient was operated upon by Dr. Wilensky, who found the spleen to be the seat of a tense cyst, rather firmly fixed to the diaphragm, and which he removed after considerable difficulty. The liver was explored and found to contain a smaller cyst in the right lobe. This was left intact for a subsequent removal.

The specimen which was sent to the laboratory consisted of a spleen somewhat elliptical and rounded, about the size of a large grapefruit almost entirely replaced by a cyst, leaving only a thin shell of splenic tissue. The cyst proper was of the typical hydatid variety, having a white chitinous thick-walled membrane, smooth on its outer aspect, and a yellowish jelly-like substance loosely attached to its inner surface. The latter was found laden with numerous scolices and hooklets. The fluid contained within the cyst had a limpid opalescent appearance.

The microscopic section shows the characteristic lamellated structure of the cyst wall with areas of calcification.

There seems to be some doubt as to whether the two types of cysts presented are caused by the same species of *Tænia*. The multilocular echinococcus was originally regarded as a colloid cancer until Virchow, in 1856, showed it to be parasitic in origin. His opinion held sway up to comparatively recent years. The Russian authority, Melinkow-Raswedenkow, working in a region where this type is almost endemic, bases his advocacy of a duality of species on various grounds, such as its peculiar growth and reproduction, its reaction to containing tissues and its somewhat restricted geographical distribution. Mangold and Müller, as a result of feeding experiments, maintain that they obtained from it a different *Tænia*, evidenced by the appearance of the hooks and the distribution of the ova.

The cases of hydatid disease recorded in the United States were first collected by Osler (1882), Sommer (1895–96), Lyon (1902), and Magath (1902–1921). In all, there were 334 cases. Using the available data up to 1902, 91 per cent. occurred in foreign born, and 9 per cent. in natives. From 1902 to 1921 Magath found only four cases who were native born Americans and from the data he had at hand he could not conclude whether all or any of these patients travelled. Professor Osler refers to only six cases of multilocular disease of the liver reported in the United States, occurring chiefly in Germans. The specimen presented to this Society is the first that I could find in the records of Mount Sinai Hospital. The multilocular variety seems to be most prevalent in Russia including East Siberia, Bavaria, Würtenberg, the adjacent districts of Switzerland and the Tyrol, whereas the hydatid variety is most commonly found in Iceland, New Zealand, Australia, Argentina and Uruguay.

The parasite is most commonly located in the liver. Vegas and Cranwell in their review of 2,027 cases of hydatid cysts arrived at the following percentages: liver (74.9 per cent.), lung (8.5 per cent.), muscle (5.7 per cent.), spleen (2.3 per cent.). kidneys (2.1 per cent.), brain (1.4 per cent.), bone (0.9 per cent.), and various other organs (4.2 per cent.). Just how the larva enters the organ it infects is not clear. However, it seems that the larva hatches in the intestine, enters the blood stream, and stops in the organ where it happens to be arrested. The frequency of liver infection also points to a possible migration by way of the common bile duct.

References

MAGATH, T. B. "Echinococcus Disease: Etiology and Laboratory Aids to Diagnosis." *Med. Clin. of North Amer.*, Sept., 1921, pp. 546–571.

MELNIKOW-RASWEDENKOW, N. "Studien über den Echinococcus alveolaris sive multilocularis," 1901 (Bibliography).

OSLER, W. "Principles and Practice of Medicine," 8th ed., 1913, p. 293.
STIRLING, E. C., AND VERCO, J. C. "Hydatid Disease." *System of Medicine*, Allbutt and Rolleston, 1909, vol. ii, part ii, pp. 870–1030.
VEGAS, M. H., AND CRANWELL, D. J. "Hydatid Cysts." *Nelson's Loose Leaf Medicine*, 1920, ii, 434–452.

TERATOID CYST OF THE HYPOPHYSIS

J. H. GLOBUS, M.D.

(From the Pathological Laboratory of the Mount Sinai Hospital, New York)

Among the cystic tumors found at the base of the brain there is a small group of cysts which are characterized by an inner lining of stratified squamous epithelium, and in which epithelial pearl-like structures, cholesterin crystals and occasionally bone are found. Through their attachment to some part of the pituitary body and because of their pressure upon the latter and the adjacent hypothalamic region, they frequently give rise to symptoms of pituitary disfunction and thus acquire in addition to histological interest a clinical significance.

Such tumors were often described as cholesteatomas, dermoids, epidermoids, and, because of occasional occurrence of cartilage or bone in their walls, they were also occasionally grouped with the teratomas.

This confusion in the classification of such cysts of the brain and its meninges was in part due to the fact that various incidental findings were accepted as fundamental features determining the character of such neoplasms. Thus the finding of the cholesterin crystals in such cysts led Mueller[1] to name them cholesteatomas, while Virchow[2] rejected this term, considering the cholesterin crystals simply an expression of a degenerative process, and preferred the old term of "Tumeurs Perlées."

For some time there was lack of agreement as to the origin of such tumors. Thus, Virchow believed them to arise from the pial connective tissue and by the process of metaplasia to gain their final histological features. Bonorden[3] thought that ectodermal tissue at the time of its invagination and formation of the "Anlage" of the anterior lobe of the hypophysis was the source of origin of such neoplasms. Beneke,[4] however, maintained that the so-called meningeal cholesteatomata took origin from the endothelial lining of the meninges. He based his claim on the fact that he was able to demonstrate by the use of silver stain a strong similarity between the epithelial cells lining the cyst cavity and endothelial cells. Later,[5] however, he revised his opinion and had accepted in part the view that some of such cysts have an epidermal derivation, this being particularly true of those cysts which contain sebaceous glands and hair. Bostroem[6] studying in greater detail meningeal and dural cholesteatomata came to definite conclusions as to the nature and origin of such cysts. He decided in favor of their epidermoid character. Erdheim[7] followed him by directing attention to a limited group of cysts which presented certain features in common, namely that they are always found at the base of the brain, in intimate connection with the pituitary body, are lined by stratified squamous epithelium and frequently contain cholesterin crystals. He traced the origin of such cysts to the embryonal rests of the subinvoluted cranio-pharyngeal duct. The latter, which is the "Anlage" of the anterior lobe of the pituitary body, does not undergo complete involution, but leaves behind small groups of epithelial cells which can be normally found on the surface of the anterior lobe of the hypophysis. These cells often give rise to tumors of the character here described. Erdheim suggested the term hypophysial duct squamous-cyst-papillomata for such tumors and separated them from the epidermoid cysts of Bostroem by pointing out some differences in their gross anatomical relationships and histological features. The epidermoids of Bostroem being true derivatives of the skin give uniformally the kerato-hyaline granular reaction in the epithelial lining and often contain hair follicles and sebaceous glands. In the hypophysial duct tumor, no kerato-hyaline granules, no sebaceous glands and no hair follicles can be demonstrated. Then again, the hypophysial duct tumors are always found in the midline at the base of the brain, back of the optic chiasm in intimate relation to the diencephalon, while the epidermoids of Bostroem may occur in any part of the brain and its meninges, and present no relation to the pituitary body.

Since Erdheim's publication of his work a number of hypophysial duct cystic tumors were reported.

D'Orsy Hecht[9] described a so-called teratoma of the hypophysis in which he found bone and epithelial structures which he considered to have been derived from the anterior lobe of the hypophysis. It would seem that the failure to find any evidence of tissue derived from entoderm would not permit his case to be included with the teratomata as the latter are by definition trigerminal in origin.[7]

Jackson,[10] Canavil and Jackson[11] and finally Duffy[12] described a number of similar tumors and have come to the conclusion that they were derived from the misplaced remnants of the ectoderm which was destined to form the anterior lobe of the hypophysis.

The case herewith reported is of interest because it presents features characteristic of the hypophysial duct neoplasms described by Erdheim. It also shows the presence of hair germs, kerato hyaline granules in the lining epithelium and sebaceous cells. Thus it appears to represent a neoplasm with structures common to both the hypophysial duct tumors of Erdheim and the epidermoid cysts of Bostroem. It would seem that there hardly can be a well-defined line of demarkation between these two groups of cysts, for apparently they have a common stem of origin.

Case L. P. No. 210957. The patient was a girl, six years of age, who had had no previous illness, and who had been quite normal up to the time of the onset of symptoms, six months before admission to the hospital. At that time she became markedly constipated; her sleep was disturbed; she became restless and lost her appetite and would experience constant thirst, demanding water very frequently. Several weeks later, on consulting a physician, the diagnosis of diabetes was made and the child was treated accordingly. With the increase of thirst and increase of water intake, there was too an increase in volume and frequency of urination. The child was losing strength, and would frequently complain of fatigue; she gave up playing, became irritable, and finally became confined to bed because of constant headaches and general weakness. A week before admission it was noted that the child's mouth was drawn to one side, and her left shoulder drooped and would frequently twitch. She was admitted to the hospital with the complaint of headache, fatigue, excessive thirst, enuresis, loss of appetite and weakness of the left shoulder.

Physical examination showed a fairly well nourished child, somewhat undersized, with a profuse growth of lanugo hairs all over the body, presenting no evidence of acute illness or mental deterioration. There was ptosis of the rght eyelid; external strabismus of the right eye due to weakness of the right internal rectus; the left pupil was larger than the right; both pupils reacted to light and accommodation. There was left facial weakness, and slight weakness of the left arm and hand; the latter was held in hemiplegic attitude. There was slight weakness of the left leg. The deep reflexes were more active on the left side, though generally reduced. There was a questionable Babinski, but gait and station were normal. The abdominal reflexes were not elicited. Spinal fluid was negative as regards cells and Wassermann. The diagnosis of neoplasm involving the posterior lobe of the pituitary and the right crus cerebri was made. The absence of distinct Babinski and the difference in abdominal reflexes indicated that the lesion was outside the substance of the peduncle.

Autopsy Findings.—(Examination of the brain only permitted.) On opening the cranial cavity the exposed dura was found to be normal in thickness and without demonstrable epidural or subdural hemorrhages. The underlying pia-arachnoid was markedly edematous and, because of the congestion of the arachnoid vessels, had acquired a purple hue. The cerebral hemispheres on the dorso-lateral surfaces showed evidence of increased intracranial pressure, the convolutions being definitely flattened and compressed. On raising the orbital surfaces of the frontal lobes, in the course of the removal of the brain from the cranial cavity, a large purple fluctuating mass presented itself at the base of the brain. It covered the optic chiasm and was adherent to the latter. Posteriorly it filled up the entire interpeduncular space. Its bulging inferior surface, which was partially free, was prolonged into a funnel-shaped process which seemed to be continuous with the pituitary body. The latter was extremely small in size, compressed, and was lodged in a shallow and eroded sella turcica. The base of the superior surface of this mass was firmly implanted in the substance of the basal surface of the brain. It occupied the entire intra-peduncular space, and because of pressure on the adjacent structures, the optic chiasm and tracts were flattened.

The tuber cinereum and the mammillary bodies could not be identified since the floor of the third ventricle was stretched and flattened by the tumor mass which almost obliterated the cavity of the third ventricle by its protrusion into it. The cerebral peduncles were displaced laterally and due to pressure were reduced in size; this was particularly pronounced on the right side. During the process of detachment of the brain from the base of the skull, the neoplasm was punctured and a dark-brown, granular, semi-fluid mass was found escaping from the cavity of the neoplasm. On opening the latter more fully, it collapsed and it was then noted that it was a rather thin-walled cyst, lined by a corrugated membrane which was beset irregularly by numerous small, glistening elevations. Cholesterin crystals were demonstrated in the contents of the cyst by the employment of specific tests. The cyst measured about four centimeters in long diameter and about three and a half centimeters in width. By its expansion and central location it had stretched markedly the vessels constituting the circle of Willis, particularly the posterior communicating and anterior cerebral vessels.

Of the cranial nerves, besides the second, the third nerve on the right side was also compressed and flattened by the neoplasm. A horizontal, longitudinal section of the brain gave a still better view of the gross structural changes that were brought about by the neoplasm. The displacement and compression of the cerebral peduncle were brought well into view and the protrusion of a cyst into the third ventricle, practically obliterating the structures on the floor, was well shown. The cavity of the cyst was fully exposed and its inner wall was disclosed. The lining of the cyst gave the appearance of a mucous coat. At the left of the anterior portion of the cyst the wall was thickening, giving rise to a tuberous elevation, cartilaginous in consistency, and somewhat translucent in appearance.

Microscopic Anatomy.—In general the wall of the cyst was for the most part uniform in thickness and showed also a more or less uniform histological structure. It was composed of three layers. The innermost coat, a layer of stratified squamous epithelium, showed at a few points some little variation in the character and maturity of its epithelium. The middle layer consisted of loose connective tissue in which were imbedded numerous glandular acini and many small ducts. The glands were strongly suggestive of being salivary in character and the ducts were lined by tall cuboidal epithelium. The lumen of these ducts was filled with a pink staining colloidal substance. The third and outermost layer was composed of a fairly thin stratum of dense fibrous connective tissue, forming a boundary between the brain tissue and the cyst as well as the outer protective wall of the exposed part of the cyst.

A careful study of this lining epithelium showed its strong resemblance to the epithelium of the dermis of a young embryo. It consists of three layers, the outer corresponding to the epitrichium, the middle intermedian layer and the lowermost, the stratum germinativum. Here and there larger collections of cells composed mainly of the germinal layer gave the appearance of hair anlages, or hair germs. Another feature of interest was the accumulation of deeply staining epithelial cells arranged in concentric layers, giving rise to structures not unlike epithelial pearls. The cells in the center of these pearls appeared to undergo degeneration, the peripheral cells having retained the structure of basal-cell epithelium and showed, when stained specifically, the characteristic intercellular bridges; when stained with Weigert's method, a blue color was imparted to these cells giving evidence of the presence of keratohyaline. These collections of epithelial cells were on the free surface of the cyst and were responsible for the small elevations that have been noted on gross examination of the tumor.

In the small cartilaginous mass in the wall of the cysts there were found several types of embryonic tissues of mesodermal origin such as embryonal cartilage, mucous connective tissue, young fibrous tissue, newly formed bone with typical bone corpuscles, calcified trabeculæ, endosteum and periosteum crowded with numerous osteoclasts, osteoblasts, osteophites, and marrow cells, filled with yellow granules which on staining with specific methods gave a typical iron reaction. In addition to these structures, there was a collection of cells arranged in long cords and supported by a fine reticulum of connective tissue. The cytoplasm of these cells was reticular in structure with the fat apparently washed out. In frozen sections, stained by specific fat stains, the cells appeared filled with large fat globules. The pycnotic character of the nuclei and the irregularity in the fat globules gave them the character of cells in sebaceous glands.

SUMMARY OF THE ANATOMICAL FINDINGS IN THE TUMOR DESCRIBED

The tumor was centrally situated, of the type of unilocular cyst, and was filled with dark-brown, coarse, granular material in which cholesterin crystals were found. Its interior was lined by corrugated mucous membrane on the surface of which were yellowish glistening papillary elevations. It bore a very intimate relationship to the hypophysis, being apparently attached to the infundibular process. Microscopically, it presented the following important features: It had a stratified squamous epithelial lining, which was embryonal in character. Here and there on the surface of the epithelial lining there was a heaping-up of cells which had a concentric lamellated arrangement, giving it the appearance of epithelial pearls. The latter were in various phases of degeneration, showing central areas of calcification, and were frequently surrounded by foreign-body giant cells. Alternating with these epithelial pearls, there were also found hair germs. Beneath this epithelial lining there was a connective tissue stroma, in which glandular tissue, salivary in character and in other places sebaceous in character, were found.

This tumor also contained embryonal cartilage, embryonal fibrous tissue, embryonic mucous connective tissue, and finally bone. The bone showed the characteristics of well-formed bone with its periosteum, endosteum, marrow cells, osteoclasts, osteoblasts, etc. It is quite conceivable in spite of all the earmarks of newly formed bone derived from misplaced bone "Anlage" that this tissue has developed by metaplasia through the degenerative process in the epithelial pearls, but it is unreasonable to believe that the cartilage tissue, the mucous embryonic tissue, the salivary gland alveoli and sebaceous cells were all and each an expression of a degenerative process. It is most probable that they were elements derived from the two germ layers, ectoderm and mesoderm, which go to make up the mature skin. Thus we may assume that we are dealing here with an autochthonous teratoid growth derived from the elements concerned in the formation of the skin and that a misplacement of such cells from the two germ layers during the period of the invagination of the ectoderm in the course of the development of the hypophysis has laid the basis for the formation of the above-described tumor.

The failure to find hair follicles or sebaceous glands in the tumors described by Erdheim as hypophysial duct tumors is, perhaps, to be ascribed to the fact that such structures have escaped recognition because of their early embryonic character.

It is also evident from the reported findings by Duffy the presence or absence of kerato-hyaline granules cannot be looked upon as an important point of differentiation between epidermoids and cysts derived from hypophysial duct, as frequently poor and prolonged fixation may interfere with the kerato-hyaline reaction.

References

1. Mueller, Johannes: Ueber den feineren Bau und die Formen der krankhaften Geschwulste. Erste Lieferung, 1838, p. 50.
2. Virchow, Rudolph: *Virchows Arch. f. path. Anat.*, 1855, viii, 371.
3. Bonorden: *Beit. z. path. Anat. u. allg. Path.*, 1892, xi, 593.
4. Beneke: *Virchows Arch. f. path. Anat.*, 1895, cxlii, 429.
5. Beneke: *Ibid.*, 1897, cxlix, 95.
6. Bostroem: *Centralbl. f. allg. Path. u. path. Anat.*, 1897, viii, 1.
7. Wilms: *Beitr. z. path. Anat. u. z. allg. Path.*, 1896, xix, 233.
8. Erdheim, J.: *Sitzungsber. d. k. Akad. d. Wissensch.*, 1904, Bd. cxiii, Heft. 10, Abt. III.
9. Hecht, D'Orsay: *Jour. Am. Med. Assn.*, 1909, liii, 13.
10. Jackson, Harry: *Ibid.*, 1916, lxvi, 1082.
11. Kanavel and Jackson: *Surg., Obst. and Gynec.*, 1918, xxvi, 61.
12. Duffy, W. C.: *Ann. Surg.*, 1920, lxxii, 537.

A CONTRIBUTION TO THE PATHOLOGY OF SUB-ACUTE EPIDEMIC ENCEPHALITIS

J. H. GLOBUS, M.D., AND I. STRAUSS, A.M., M.D.

(From the Pathological Department, Mount Sinai Hospital, New York City)

In the literature we find abundant and accurate descriptions of the neuropathological findings in acute epidemic ("lethargic") encephalitis. Following the lead of Von Economo[1] a large number of investigators--Marinesco,[2] Bassoe and Hassin,[3] Wegeforth and Ayer,[4] Neal,[5] and others—have recorded their observations on the gross and microscopic changes in the central nervous system caused by this disease. In their accounts of the lesions found in acute epidemic encephalitis, they refer generally to anatomical changes common to and characteristic of the acute form of the disease which are universally expressed in terms of perivascular infiltrations, a moderate amount of neuronophagia, a mild degree of glia proliferation, and occasionally hemorrhagic foci. It is further emphasized by them that the above changes are most commonly and most constantly found in the region of the midbrain and basal ganglia, not, however, to the complete exclusion of lesions in other parts of the central nervous system. Thus, lesions in the cerebral cortex (Hassin),[6] spinal cord (Calhoun),[7] and peripheral nerves (Burrows)[8] have been described as occurring in acute epidemic encephalitis.

However, it is quite evident that, in spite of their abundance, the above-quoted observations do not exhaust the subject of the histopathology of acute epidemic encephalitis.

Von Economo[9] has already reported a case which he called "chronic intermittently progressive lethargic encephalitis." His patient insidiously developed an atypical form of lethargic encephalitis which was characterized by alternate episodes of delirium and lethargy, dysarthria and slight pyramidal tract involvement. This condition remained unchanged for two months, and was followed by partial improvement. Later in the course of the disease there developed dysphagia, paresis of the tongue leading to gradual debility of the patient and terminating in death a year and a half after the time of the onset of the disease.

Von Economo concluded that his patient was suffering from a chronic epidemic encephalitic process, to which new features were added in the terminal stage of the disease.

The anatomical changes which were associated with the lesions incurred during the early, acute period of the disease were (*a*) areas of softening with or without accumulations of granular cells; (*b*) bands of dense glia fibers; (*c*) small collections of glia cells, apparently cells which were at one time concerned with the process of neuronophagia; and finally (*d*) mild degenerative changes in the axis cylinders of long projection tracts. Among the new features he emphasizes recent perivascular hemorrhages, degenerative changes in ganglion cells, and perivascular infiltrations. He suggested that the recrudescence of the disease was probably due to incomplete elimination of the virus during the early period of the disease, and that a highly suggestive analogy was thus established between chronic progressive muscular atrophy in its relation to acute anterior poliomyelitis and this chronic form of lethargic encephalitis in its relation to acute epidemic encephalitis. It would appear from the clinical history of von Economo's case that an attempt towards healing must have occurred in the course of the disease, and it was apparently his aim to demonstrate this fact, but his histological descriptions fail to show any reparative change in the brain—the lesions described such as softening, accumulation of granular cells and extravasations pointing mainly to a lesion of destructive character.

In this regard, the findings in the group of cases reported in this paper demonstrate an important departure from the observations of von Economo, for we are in a position to demonstrate changes in the central nervous system that mark a well-defined tendency toward repair.

This series of cases might clinically be grouped with the mild protracted forms of lethargic encephalitis and could be termed subacute epidemic encephalitis. Early in their course they showed a well-defined tendency toward recovery, then remained stationary for a variable length of time, finally to suffer a new insult leading into the acute, rapidly fatal, virulent form of the disease.

The important feature of this group of cases is the changes found occurring in the small cerebral vessels, indicative of an attempt on the part of the vascular system to repair the damage which occurred during the acute stage. The exacerbation of the disease, however, damaged the blood vessels, arrested the progress of repair, and this phase of the healing process became fixed.

Clinical Observations: It is not our aim to give a detailed account of the various clinical manifestations which have been observed in each of the four cases studied. A summary of the more constant and outstanding features common to all members of this group will be given. All of the patients studied have given a history of having had at one time a mild form of influenza in the course of the year preceding the onset of the apparently acute symptoms. They were admitted to the hospital complaining of general weakness, a variable amount of paresis and mild ocular symptoms. The clinical course during their residence in the hospital was marked at first by a tendency toward recovery, and improvement in their subjective and objective symptoms. This improvement, however, did not progress very far, and the condition became stationary. It is during this period that there occurred a sudden change; the patient became suddenly acutely ill, giving evidence of marked dyspnea, complete ocular palsies, dysphagia, and dysarthria. This apparently was the fatal turning in the course of events, as death took place soon after the onset of the acute recrudescence of the disease.

These striking features in the clinical course were paralleled by the anatomical changes to be described. It will be seen that lesions expressive of the three phases above noted in the clinical course of the disease can be demonstrated in the pathological material studied. Thus we shall find changes which are indicative of the early mild stage alongside of lesions suggestive of the reparative tendencies, and finally areas of destructive processes mark the final acute and fatal outcome of the disease.

Autopsy Findings: The gross anatomical changes consisted mainly of extreme congestion of the pial vessels, particularly over the ventral surface of the medulla and pons. No definite meningeal hemorrhages were noted in any of the four cases. Small petechial hemorrhagic foci, however, were seen on sectioning of the brains. The larger vessels at the base were followed out in their course to the smaller branches, and no arteriosclerotic changes could be found. The consistency and topography of the brains examined showed no abnormalities of note.

Microscopic Findings: In the course of the histological studies, a thorough search was made for minute anatomical changes throughout the brain stem, cerebral and cerebellar cortex. Particular care was exercised in the examination of the sections from the mid brain, basal ganglia and medulla, as the more important changes were anticipated there.

In general, it may be said, and this is highly significant, that lesions typical of the acute form of epidemic encephalitis were not conspicuous; nevertheless, in the vicinity of the aqueduct of Sylvius and in the medulla vessels were found showing the typical small round cell, adventitial infiltration. The most frequent findings throughout the brain stem were numerous perivascular and extravascular hemorrhages. That these hemorrhages were not agonal was shown by the presence of blood pigment in the adventitial spaces of blood vessels in parts remote from the seat of the extravasation of blood. Wherever such hemorrhages have occurred the walls of vessels involved showed no thickening or perivascular infiltration. Apparently these vessels were spared in the first attack of the disease and during the exacerbation of the disease the adventitia of these vessels was damaged to such an extent that it was incapable of proliferative changes and could not withstand the pressure of vascular engorgement. These hemorrhages were most extensive and most frequent in the medulla, this being noteworthy in its bearing on the clinical course of the disease. Another frequent finding was the small accumulations of glia cells in groups of five or eight cells about ganglion cells undergoing neuronophagia.

Further evidence of an extensive degenerative process in the brain was found in the wide distribution of fat granules and globules in the cells of the adventitial coat of the vessels throughout the brain stem, and to a slight degree in other parts of the central nervous system.

Glia changes were also expressed as mild forms of proliferation and mobilization about blood vessels, in the subependymal layer in the floor of the fourth ventricle and of the aqueduct of Sylvius, and in the accumulations already described above. Only arterioles and capillaries were apparently singled out by the glia cells in their proliferative aggregation, and this fact coupled with adventitial changes in the smaller vessels constitute the most important pathological changes observed.

It was already pointed out that only close scrutiny yielded here and there a vessel with typical perivascular infiltration amid widespread perivascular and extravascular hemorrhages, while organization in the adventitial coat of the smaller vessels and capillaries was the most obvious and generalized change in the structure of the involved areas of the brain stem.

Apparently the perivascular, lymphocytic infiltration, which is the early anatomical manifestation of the disease, here gave place, through the proliferation and metamorphosis of lymphocytic elements and adventitial cells, to fibroblasts which thickened considerably the walls of the vessels. Further advance toward a distinct periarteritis was made through the progress of the same process of metamorphosis of the elements of perivascular infiltration. This is apparent in the thickening of the adventitia which is extremely rich in fibrous elements, though numerous lymphocytes are still found in the fibrous meshwork.

More striking, however, are the changes in the small capillaries of the involved areas, particularly in the gray substance about the aqueduct of Sylvius. They are expressed in the swelling and proliferation of the adventitial cells and the swelling of the intimal endothelial cells. This feature was often so pronounced as to obliterate almost completely the lumen of the vessel.

Small vessels which are only moderately thickened were seen frequently surrounded by glia cells, a few lymphocytes and an occasional granular cell.

Microscopic examination of the vessels aided by specific stains such as resorcin-fuchsin, Van Gieson and Sudan III disclosed no features pointing to arteriosclerosis. Elastic membranes were intact; there was no splitting of the latter, no deposits of hyalinizing placques and no calcification in the intima or media.

The pia-arachnoid appeared normal except in a few small areas where it was distinctly thickened and presented features of organization such as the presence of many fibroblasts, small, newly formed blood vessels and lymphocytes.

Significance of the Histological Changes: It is evident that the modification of the structure of the small vessels forms the essential pathologic change. We believe that the primary attack of the virus is upon the wall of the small and medium-sized vessels, and that the vessel wall is affected by the virus in a manner proportionate to its virulence.

It is our opinion that many of the elements of the perivascular infiltration have their ultimate origin in the Virchow-Robin's space—cells often referred to by other writers as endothelial cells. These cells, characterized by a large amount of cytoplasm and clear vesicular nuclei, were found to be the predominating element in our preparations, and were frequently found in various stages of cell division.

It appears to us, then, that production of elements of infiltration, destined perhaps to repair damage occurring in the immediate vicinity of the vessel, is an important function of the adventitia. Thus, when the virus or even a mineral poison reaches the adventitia, it reacts by formation of adventitial elements, provided that the vessel wall is not damaged to an extent of losing its potency for adventitial proliferation. Should the virus or toxin, however, be so destructive to the vessel wall as to incapacitate it for cell proliferation and weaken it so it could not withstand the pressure of vascular engorgement, then perivascular hemorrhages will occur in large numbers, a feature characteristic of the acute, virulent type of the disease.

The reverse is also true, for when the virus reaches the vessel in a small amount or in attenuated form, changes pointing to subacute lesions follow, as was shown in our case.

Such interpretation of the histologic changes in the brain led us to suggest the grouping of acute epidemic encephalitis into:

1. An acute infiltrative form, with the dominant feature of perivascular infiltration.
2. An acute hemorrhagic form, where the virulence of the disease is expressed in numerous extensive hemorrhages.
3. A subacute productive form, as described in this paper

The acute infiltrative is the early stage of any acute form of acute epidemic encephalitis which may resolve itself rapidly into the fatal hemorrhagic type or the protracted, mild productive form.

References

1. von Economo, C.: *Wien. klin. Wchnschr.*, 1917, xxx, 581.
Ibid., 1918, xxxi, 850.
2. Marinesco, G.: *Bull. de L'Acad. de Méd., Par.* lxxx, 411.
3. Bassoe, P., and Hassin, G. B.: *Arch. Neurol. and Psychiat.*, 1919, ii, 24.
4. Wegeforth, P., and Ayer, James B.: *Jour. Am. Med. Assn.*, 1919, lxxiii, 5.
5. Neal, J. B.: *Arch. Neurol. and Psychiat.*, 1919, ii, 271.
6. Hassin, G. B.: *Jour. Nerv. and Ment. Dis.*, 1921, liii, 27.
7. Calhoun, H. A.: *Arch. Neurol. and Psychiat.*, 1920, iii, 1.
8. Burrows, M. J.: *Arch. Int. Med.*, 1920, xxvi, 477.
9. von Economo, G.: *München. med. Wchnschr.*, 1919, xlvi, 1311.

Volume XXI, 1921

INDEX

A

Actinomycosis, human, two cases of. Paul F. Russell 143
Alexander, Harry L., Larsen, Nils P., and Paddock, Royce. The skin reaction in bronchial asthma and allied conditions . 135
Aneurysm of the hepatic artery. William Friedman 177
Appendix, fibrosarcoma of. George L. Rohdenburg 83
Aschner, P. W. Tumors (3) of the kidney pelvis and of the ureter 175
Asthma, bronchial, and allied conditions, skin reaction in. Nils P. Larsen, Royce Paddock, and Harry L. Alexander 135
Auricle, left, a tumor of. P. D. Hoffman 85

B

Bacteriophage reaction of d'Herelle. Abraham Zingher 2
Basedow's disease, technique of complement fixation reaction in. John Koopman 56
Berkeley, William N. A complement fixation test of value in the clinical diagnosis of toxic thyroid states 51
Blood chemical changes in, in nephritis. Victor C. Myers . 25
Blood, significant chemical changes in, in the toxemias of pregnancy. John A. Killian 29
Bone, diffuse endothelioma of. James Ewing 17
Brain tumors, three. Nathaniel B. Stanton 77

C

Calcification of the pericardium. A. Winkelstein 181
Cecil, Russel L., and Steffen, Gustave I. Active immunity against experimental pneumococcus type I pneumonia, in monkeys, following intratracheal injection of vaccine 132
Complement fixation reaction, technique of, in Basedow's disease. John Koopman 56
Complement fixation test of value in the clinical diagnosis of toxic thyroid states. William N. Berkeley 51
Cooke, Robert A. Cutaneous reactions in human hypersensitiveness 8
Cutaneous reactions in human hypersensitiveness. Robert A. Cooke 8

E

Echinococcus, hydatid, of spleen. Leo Edelman 185
Echinococcus, multilocular, of liver. Leo Edelman 185
Edelman, Leo. Hydatid echinococcus of the spleen 185
Edelman, Leo. Multilocular echinococcus of the liver 185

Encephalitis, subacute epidemic, a contribution to the pathology of. J. H. GLOBUS AND I. STRAUSS 195
Endocrine gland studies, including goiter, in India. ROBERT McCARRISON 154
Endothelioma, diffuse, of bone. JAMES EWING 17
Epithelioma of the esophagus, and metastasizing hepatoma, the simultaneous occurrence of. DE WITT STETTEN 42
EWING, JAMES. Diffuse endothelioma of bone 17

F

Fibrosarcoma of appendix. GEORGE L. ROHDENBURG 83
FLOYD, ROLFE. Probable syphilitic interstitial pneumonia in an adult 58
FRASER, ALEXANDER. Two cases of congenital lesions of the heart 91
FRASER, ALEXANDER. Typhoid lesions of the kidney 95
FRIEDMAN, WILLIAM. Aneurysm of the hepatic artery 177

G

GLOBUS, J. H. Teratoid cyst of the hypophysis 188
GLOBUS, J. H., AND STRAUSS, I. A contribution to the pathology of subacute epidemic encephalitis 195

H

Heart, two cases of congenital lesions of. ALEXANDER FRASER 91
Hepatic artery, aneurysm of. WILLIAM FRIEDMAN 177
Hepatoma, metastasizing, and an epithelioma of the esophagus, the simultaneous occurrence of. DE WITT STETTEN 42
HOFFMAN, P. D. A tumor of the left auricle 85
Hyperplasia of the parathyroid glands in rickets. JOHN MINOR AND A. M. PAPPENHEIMER 98
Hypersensitiveness, human, cutaneous reactions in. ROBERT A. COOKE 8
Hypophysis, teratoid cyst of the. J. H. GLOBUS 188

I

Immunity, active, against experimental pneumococcus type I pneumonia in monkeys following intratracheal injection of vaccine. RUSSELL L. CECIL AND GUSTAVE I. STEFFEN 132

K

Kidney pelvis and ureter, three tumors of the. P. W. ASCHNER 175
Kidney, typhoid lesions of the. ALEXANDER FRASER 95
KILLIAN, JOHN A. Significant chemical changes in the blood in the toxemias of pregnancy 29
KOOPMAN, JOHN. Technique of complement fixation reaction in Basedow's disease 56

L

LARSEN, NILS P., PADDOCK, ROYCE, AND ALEXANDER, HARRY L. The skin reaction in bronchial asthma and allied conditions 135
Leptospira icteroides, demonstration of, with notes of the result of prophylaxis and serum treatment in yellow fever. HIDEYO NOGUCHI 49
Lipoma of the uterus. ROBERT C. SCHLEUSSNER 33
Liver, multilocular echinococcus of the. LEO EDELMAN 185

Liver, primary spindle-cell sarcoma of the, associated with cirrhosis. Morton Ryder 113

Lung, malignant tumors of the. A. V. St. George 65

M

Martland, H. S. Primary bone tumors: Their classification with special reference to benign giant-cell tumor 102

McCarrison, Robert. Endocrine gland studies, including goiter, in India 154

Minor, John, and Pappenheimer, A. M. Hyperplasia of the parathyroid glands in rickets 98

Myers, Victor C. Chemical changes in the blood in nephritis 25

N

Nephritis, chemical changes in the blood in. Victor C. Myers 25

Noguchi, Hideyo. Demonstration of *Leptospira icteroides*, with notes of the results of prophylaxis and serum treatment of yellow fever 49

P

Paddock, Royce, Larsen, Nils P., and Alexander, Harry L. The skin reaction in bronchial asthma and allied conditions .. 135

Pappenheimer, A. M., and Minor, John. Hyperplasia of the parathyroid glands in rickets 98

Pathology of subacute epidemic encephalitis. J. H. Globus and I. Strauss 195

Pericardium, calcification of the. A. Winkelstein 181

Perlzweig, William A. Preliminary report on the nature of the immunizing antigen of pneumococcus type I 133

Phage (lytic agent) isolated from transplantable animal tumors. George L. Rohdenburg 38

Pneumococcus type I, preliminary report on the nature of the immunizing antigen of. William A. Perlzweig 133

Pneumonia, experimental pneumococcus type I, active immunity against, in monkeys following intratracheal injection of vaccine. Russell L. Cecil and Gustave I. Steffen 132

Pneumonia, probable syphilitic interstitial, in an adult. Rolfe Floyd 58

R

Rickets, hyperplasia of the parathyroid glands in. John Minor and A. M. Pappenheimer 98

Rohdenburg, George L. Concerning a phage (lytic agent) isolated from transplantable animal tumors 38

Rohdenburg, George L. Fibrosarcoma of the appendix 83

Russell, Paul F. Two cases of human actinomycosis 143

Ryder, Morton. Primary spindle-cell sarcoma of the liver associated with cirrhosis 113

S

Sarcoma, primary spindle-cell, of the liver, associated with cirrhosis. Morton Ryder 113

Schleussner, Robert C. Lipoma of the uterus 33

Skin reaction in bronchial asthma and allied conditions. Nils P. Larsen, Royce Paddock, and Harry L. Alexander 135

Spleen, hydatid echinococcus of the. LEO EDELMAN 185
ST. GEORGE, A. V. Malignant tumors of the lung 65
STANTON, NATHANIEL B. Three brain tumors 77
STEFFEN, GUSTAVE I., AND CECIL, RUSSELL L. Active immunity against experimental pneumococcus type I pneumonia in monkeys following intratracheal injection of vaccine 132
STETTEN, DE WITT. The simultaneous occurrence of a metastasizing hepatoma and an epithelioma of the esophagus 42
STRAUSS, I., AND GLOBUS, J. H. A contribution to the pathology of subacute epidemic encephalitis 195

T

Teratoid cyst of the hypophysis. J. H. GLOBUS 188
Thyroid states, toxic, a complement fixation test of value in the clinical diagnosis of. WILLIAM N. BERKELEY 51
Toxemias of pregnancy, significant chemical changes in the blood in. JOHN A. KILLIAN .. 29
Tumors, brain, three. NATHANIEL B. STANTON 77
Tumors, irritation, a reply to Dr. Johannes Fibiger on the subject of. FRANCIS CARTER WOOD 122
Tumors, malignant, of the lung. A. V. ST. GEORGE 65
Tumor of the left auricle. P. D. HOFFMAN 85
Tumors, primary bone; their classification with special reference to benign giant-cell tumor. H. S. MARTLAND 102
Tumors (three) of the kidney pelvis and of the ureter. P. W. ASCHNER 175
Typhoid lesions of the kidney. ALEXANDER FRASER 95

U

Uterus, lipoma of the. ROBERT C. SCHLEUSSNER 33

W

WINKELSTEIN, A. Calcification of the pericardium 181
WOOD, FRANCIS CARTER. A reply to Dr. Johannes Fibiger on the subject of irritation tumors 122

Y

Yellow fever, demonstration of *Leptospira icteroides,* with notes of the results of prophylaxis and serum treatment of. HIDEYO NOGUCHI 49

Z

ZINGHER, ABRAHAM. The bacteriophage reaction of d'Herelle 2

RB
1
N32
n.s.
v.19-21
Biological
& Medical
Serials

New York Pathological Society
Proceedings

PLEASE DO NOT REMOVE
CARDS OR SLIPS FROM THIS POCKET

UNIVERSITY OF TORONTO LIBRARY